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CONTENTS.

Contents—(*Continued*).

CONGENITAL OCCLUSION OF THE DUODENUM [1]

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With Plate 19

Definition. By Congenital Occlusion of the Duodenum is meant a partial or complete interruption of the lumen of the bowel, usually situated in the vicinity of the opening of the bile duct. The occlusion may result from developmental errors or from antenatal disease.

Historical. The condition is somewhat rare. The earliest writing on the subject is by Aubéry in 1805. In 1812 Meckel quotes three fresh cases together with one case of his own. In 1837 Billiard, in his great work on children, describes a fresh case with a case described by Schäfer in 1824. In this year Rokitansky also fully describes a case of his own. Theremin, in 1877, writing on atresias of the alimentary canal, gives seven cases. He emphasizes the rarity of the condition: in 111,401 births there were two examples of the abnormality. In the lying-in hospitals of St. Petersburg 9 cases had occurred, but in Moscow and Prague the condition had never been found. Gaertner, in 1883, collected 16 cases and gives most of the literature up to date. Champneys, in 1897, showed a good specimen before the Pathological Society of London, but in his paper no extensive references are given.

The first recent paper which is at all comprehensive is by Cordes in 1901. He tabulates and analyses 57 cases with minute care. Kuliga, in 1903, collected 185 cases of stricture of the alimentary canal; in 59 of these the duodenum was affected. Operative treatment was mentioned by Ucke of St. Petersburg in 1907, but none of the latest papers have echoed his suggestion, and the operation of gastro-enterostomy has not yet been attempted. The papers mentioned are the chief ones on the subject; the most important are those by Cordes (57 cases) and Kuliga. At other times many observers have described isolated cases, so that now I have been able to collect 92 cases for analysis.

Clinical picture. This is best described by reference to the notes of a case recently observed.

The patient, a male child of $5\frac{1}{4}$ lb., was born on March 16, 1911, four weeks before full term. It seemed as well nourished as usual for its size. The parents were healthy; the mother had previously given birth to ten healthy children.

Within two hours of its birth the child was vomiting vigorously. The

vomit was dark in colour from the first and consisted of 'coffee grounds' material. There was never mucus ejected in any quantity. A few hours later the bowels were well open and a large meconium stool passed.

Haematemesis continued for fifty hours at gradually increasing intervals. The infant became weak and finally died 52 hours from birth. The motions were normal—contained no blood—normal urine was also passed, and beyond small feeds, which were immediately vomited, no treatment was adopted. On physical examination, the abdomen was distended in the upper part; no mass was felt. In this case peristalsis was not visible.

No definite diagnosis was arrived at. Purpura neonatorum was negatived on account of these facts : (1) Vomiting began two hours after birth. Thirty to forty hours is the common time for haematemesis neonatorum to commence. (2) Absence of bleeding from bowel and skin or mucous membranes.

Post-mortem. The abdomen was somewhat distended. When opened the greatly distended stomach immediately attracted attention. The stomach and first part of the duodenum were greatly dilated. The pylorus was easily distinguished by a groove. The stomach preserved its usual outline, while the dilated duodenum formed a globular sac which pressed upwards on to the gall-bladder. Just above the opening of the common bile duct the spherical distension ended abruptly in a narrow cord. Beyond this the rest of the duodenum continued in a perfectly normal fashion. The pancreas, liver, and spleen were normal. The remainder of the bowel was quite normal, containing meconium. The meconium presented the usual microscopical appearance, except that no hairs were seen.

The following measurements were taken after hardening. A list of measurements in a thirty-six weeks child of the same weight is given for comparison.

Stomach.

Length from cardia to pylorus (great curvature) . . .	16 cm.	Usual length 9 cm.
Maximum circumference . .	11·5 cm.	,, ,, 7 cm.
Circumference of pylorus . .	4·5 cm.	., ,, 3·2 cm.

Duodenum.

Length from pylorus to occlusion (lower curvature) . . .	10·2 cm.
Maximum circumference . .	11 cm.
Circumference of occluded portion	9 cm.
Circumference of second portion .	2 cm.

On section the stomach and duodenum were distended with gas, but also contained about half a drachm of 'coffee grounds' material mixed with watery secretion. No bleeding-point was seen, but proper steps to find an ulcer were not taken. (The stomach was not opened and pinned out before hardening.) The first part of the duodenum ended in a little blind dimple. On dissection the common bile duct was seen opening coincidently with the pancreatic duct a short distance below the stricture. Two longitudinal folds of mucous membrane ran up the posterior wall of the duodenum. They increased in size and gradually diverged as they reached the neighbourhood of the bile papilla. At this point each fold became very marked and turned sharply outwards to meet the lateral walls of the duodenum. The folds presented free edges ; arching outwards they practically met beneath the anterior wall, but left a small tunnel on the posterior wall. This led into a space which rapidly narrowed until the bowel was no longer pervious. A small fold in this space contained the opening of the bile duct. Section of this portion showed the whole diameter much diminished

and muscular walls increasing in thickness as the lumen diminished till the whole formed a small solid rod.

Length of strictured portion	1·1 cm.
Length of solid cord	0·5 cm.
Circumference	0·9 cm.

Analysis of Recorded Cases.

Cordes has made a careful analysis of the collected cases of his series. The results of the additional 35 cases are given below.

Sex. My figures show 8 male and 8 female, the sex is not mentioned in 19. In the whole series there are 21 males, 22 females, and 49 doubtful cases.

Frequency and nature of vomit.

	Cordes's cases.	Fresh series collected.	Total.
Vomiting present	41	13	54
Not recorded	16	22	38
Blood, old or recent	27	7	34
Bile	2	2	4
Food	2	—	2
? Nature	10	4	14

Position of occlusion.

	Cordes.	Fresh series.	Total.
Above opening of common duct	20	11	31
Below opening	13	7	20
Level with	6	3	9
Not mentioned	18	14	32

Presence of other abnormalities in the alimentary canal.

None beside duodenal occlusion .	54 cases.
Stenosis of other parts of bowel .	8 cases.
Foetal peritonitis	3 cases.
Enlarged liver and spleen .	1 case.

Pathology.

Position of occlusion. In the table prepared from the study of all the recorded cases the situation is accurately mentioned in 60. The common bile duct opens above in 31 cases, below in 20, and on a level with the occlusion in 20 cases. The Vaterian segment is the commonest portion of the duodenum affected. One would have expected this result, since this is the situation of so many important embryological events. Here the liver and pancreatic buds grow out, the lumen is at one time occluded, and the morphological fore-gut becomes the mid-gut.

Date at which occlusion occurs. In discussing the source of the stricture we shall see that certain changes occur before the second month of intra-uterine life which greatly help in the explanation of the formation of this condition. In a large number of cases in which the septum is below the common bile duct normal meconium is present in the bowel. This shows that the stricture was formed after the third month, when bile begins to be formed. In the present case the occluded portion measured 0·9 cm. in circumference, while the rest of the duodenum was 2 cm. There was no evidence of any gross disease having caused the difference in size. Supposing at this point this portion of duodenum ceased to grow, then by comparison with other foetuses we should be able to time the occlusion. Unfortunately I have not been able to obtain such data at present.

Source of the occlusion. There are two possible methods by which such an occlusion may arise: (1) By an error of development; (2) As the result of definite antenatal pathological processes. In the majority of cases no actual cause can be discovered, and an explanation is sought by means of developmental theories. Tandler has very carefully studied the development of the Vaterian segment of the duodenum in embryos of from thirty to sixty days. In his series the lumen of the gut is clear in the youngest and oldest embryos, but in the intermediate stages becomes blocked by a cellular proliferation. It is easy to see how a complete or partial failure of this plug to absorb can account for any grade of occlusion. The difficulty, if we accept this view of the pathogenesis of the condition, is to reconcile the dates of this cellular proliferation and the excretion of bile. In a small proportion of the cases a definite cause for the condition can be assigned.

Foetal volvulus. At one time this was the favourite explanation of the occlusion. Kutner (1857), in considering his case, dismisses volvulus and says there is no evidence for this explanation. Rokitansky, Schottelius, and Gaertner all quote cases, but the evidence is poor. Kuliga (1903) says that in one or two of the undoubted volvulus cases, the volvulus is the result and not the cause of the occlusion. Gross (1905) describes a very interesting case of a newborn infant with a mesoduodenum. The rotation of this portion of the bowel had not occurred, and the duodenum hung as a movable loop, so that no attempt at volvulus, however, was present. Claremont (1905) found in an adult a duodenum completely twisted on itself, but no obstruction was present.

Foetal peritonitis. Cases where the occlusion has undoubtedly been due to adhesions in foetal peritonitis are quoted by Theremin, Hirschsprung, v. Dohrn, Fielder, and Gaertner. Silbermann, in his study of foetal peritonitis, however, finds that it is very rare to see an associated stenosis of the bowel. Volvulus is sometimes associated with this condition; cases are described by Fielder, Wiederhofer, Schottelius, and Mauclaire.

Rarer causes of occlusion of the duodenum. These causes are so rare that they become merely pathological curiosities. Wyss and Hammer have described hypertrophy of valvulae conniventes causing obstruction. Baillie, in

1827, wrote of a case where he found in an adult a very large valvula connivens almost occluding the bowel. Hess met with a case apparently due to compression by the mesocolon. Nobiling found the bowel strangulated by a loop of the omphalo-mesenteric artery. Schott and Wünsche respectively found a cyst in the iliac fossa and an inguinal hernia pulling on the mesentery. Hirschsprung and Sever found cases where the head of the pancreas seemed press on the bowel. Wiederhofer described an antenatal carcinoma of the liver, and Kristella a large liver pressing on the bowel.

Why does the stomach dilate? The dilatation of parts above the stricture is generally a marked feature of the case. The pylorus becomes marked as a groove. Some of the earlier authors failed to recognize this fact, and spoke of a bilocular stomach. In cases where the condition is found in stillborn infants the stomach is full of mucus or watery fluid, while in the cases born alive large quantities of fluid are usually vomited from the very first. The presence of this fluid is probably the cause of the dilatation. The mucosa-lined muscular sac secretes fluid under pressure and dilates in just the same way as does a gall-bladder with obstructed duct. The dilated stomach may in fact be looked upon as a mucocele.

Source of the bleeding. Haematemesis occurs in about 65 per cent. of the collected cases. The exact cause of the bleeding, however, is not clear. In my case the presence of an ulcer cannot be absolutely excluded, since the stomach was not opened and pinned out at once after death. In the case of Schütz a tiny erosion was actually discovered and the opening into the vessel was found plugged with a recent clot. The entire portal system appears to be congested in a good many of the cases. In the photograph shown the vessels stand out clearly. No bleeding occurred from the mucosa below the stricture, however, while the dilated portion above was full of blood, so that simple portal congestion will not account for the bleeding. In the majority of cases there is haematemesis from the first. Occasionally, however, mucus is first vomited, and only later as the vomiting continues does blood appear. In the case of Funck-Brentano, the child vomited mucus, then material streaked with blood, and finally large quantities of blood. The conclusion is, therefore, that in most of these cases the gastrorrhagia is mechanical in origin, resulting from the strain of vomiting on an already over-distended stomach.

Diagnosis.

The points on which a diagnosis can be made are quite definite. *Vomiting.* In all the cases where vomiting is mentioned at all it is recorded as being present, so that in fifty-four cases vomiting was present: the point is not mentioned in thirty-eight. The vomiting usually begins at once after birth: the material is forcibly ejected and is got rid of in large quantities. *Haematemesis* occurs in about 65 per cent. of the cases. The bleeding differs from that of purpura neonatorum in that it usually comes on almost at once after birth, and is not

accompanied by melaena or other evidence of purpura. Although the vomiting is persistent and severe, yet usually the bowels are well open and normal meconium is passed. In occlusions of the bowel lower down constipation is usually absolute. *Of physical signs.* The upper abdomen is distended; sometimes peristalsis may be seen. Cyanosis is usually present, since the diaphragmatic action is so impeded. Bismuth given for X-ray diagnosis has not yet been tried, but should prove a useful aid in these cases.

Treatment.

The condition has been so little recognized that but scanty opportunity for treatment has arisen. In the few cases where a diagnosis has been made, lavage has been tried. Five cases have been subjected to laparotomy, those of Wyss, Simmonds, Hess, Kirmisson, and Schütz. Enterostomy has been attempted in each of these cases, but in none has the infant survived more than a few hours. Ucke of St. Petersburg, in 1907, suggested gastro-enterostomy, but this has not yet been carried out. As far back as 1899 Abel performed a successful gastro-enterostomy on an eight-weeks-old infant for hypertrophic pyloric stenosis (the time of operation was forty minutes). So that with the present-day improvements in technique this operation should be at least considered justifiable to attempt. In more than half the cases available for analysis the opening of the common bile duct was below the stricture, so that in a gastro-enterostomy there is not a great risk of trouble from this source. In about ten per cent. of the cases some other deformity exists, as multiple stenosis of small intestine, absence of anus, and so on. In these cases the clinical picture characteristic of occlusion of the duodenum, vomiting normal action of the bowel, does not obtain. The infants live a variable time with complete occlusion. Death usually takes place on the fourth or fifth day. The longest life is nine months (quoted by Keith). With partial stenosis one case lived as long as eighteen months (Buchannan). From the consideration of these facts it would seem that the cases should be subjected to laparotomy, and if possible gastro-enterostomy should then be performed.

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DESCRIPTION OF FIGURES.

Fig. 1. View from the front, showing dilated stomach and duodenum.

Fig. 2. Tracing from photograph of anterior view of viscera. The size of a normal stomach and duodenum is represented by the dotted line.

Fig. 3. View from behind entrance of bile and pancreatic ducts just below occlusion. D^i. First portion of duodenum. D^{ii}. Second portion of duodenum. Between these two parts is seen the bile duct B opening just beyond the stricture.

Fig. 4. Diagram of site of atresia magnified about three times. (a) First portion of duodenum in blind pit. (b) Cord-like portion above opening of common bile duct. (c) Normal second portion, with longitudinal folds. (d) Common opening of bile and pancreatic ducts.

Fig. 5. Diagrammatic sections taken from below upwards ($\times 3$). I. The two folds. II. Turning outwards before reaching the bile duct. III. The bile duct. IV. Just above bile duct.

FIBRILLATION OF THE AURICLES: ITS EFFECTS UPON THE CIRCULATION.*

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PLATES 43 AND 44.

A little more than two years ago, while working at a peculiar form of heart irregularity exhibited by human subjects, which had been described by Mackenzie[1] as "nodal rhythm," I was able to bring forward considerable evidence[2] to show that the irregularity in question results from fibrillation of the auricles. The evidence for that conclusion was based upon a comparison of curves taken by several methods from the human subject and the experimental heart. The similarity of electrocardiograms taken from patients, and from dogs in which auricular fibrillation had been induced, was noticed almost simultaneously by Rothberger and Winterberg.[3] A fuller analysis of these electrocardiograms supported the hypothesis; and the contention was finally proved by the observation that the oscillations characterizing the clinical electric curves arise from the auricular portion of the heart, and especially by the observation that a similar irregularity occurs in the horse and that this irregularity may be shown by inspection of the heart in that animal to result from auricular fibrillation.[4] Briefly, it has been shown that the commonest form of irregular heart action in man is due to this disturbance of the auricular mechanism. The irregularity is of

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this form in 70 per cent. of all cases of heart failure, as I have been able to demonstrate by electrocardiographic curves taken from over a hundred patients. The conclusion is now generally accepted.

The disturbances of the circulation are so profound in the human subject, when this curious disorder of the heart's action begins, that further study of them seemed desirable. With this object in view, I have undertaken the experiments described in the present communication.

PRELIMINARY OBSERVATIONS UPON METHOD.

The observations have been carried out upon a number of cats and dogs; the former were anesthetized with urethane and ether, the latter with morphia, paraldehyde, and ether. Fibrillation of the auricles was induced by faradic stimulation of the right auricle. In order that the heart should be surrounded by conditions as natural as possible, the stimulation was performed with the chest wall restored, wherever the circumstances of the experiment permitted such restoration. A small window was made in the chest wall over the right auricle, and small flexible electrodes of the fish hook type were fastened into

TEXT-FIG. 1. Cat 30. A kymographic curve, showing the effects on arterial and venous blood pressures of faradization of the right auricle. The actual readings of the venous manometer are written on the curve. A subtraction of 174 mm. must be made to arrive at the actual venous pressure in mm. of magnesium sulphate (specific gravity, 1,046).

TABLE I.

Arterial Pressure.
The Effect of Auricular Fibrillation in Cats. The Figures
Represent the Actual Rises and Falls.

Cat.	Onset.	After first few seconds.	After second few seconds.	Offset.	Remarks.
28	−24	+10	+10	0	
	−36	+16	0	+20[5]	
29	0	0	0	0	
	−10	0	+ 4	+ 6	
30	+20	− 8	0	−12	Rate during fibrillation 102 only.
	−25	+ 8	+ 8	+16	
	−24	+10	0	+ 8	
32	0	0	0	0	
	−20	+18	0	+ 8	
31	− 2	0	0	+ 2	Heart exposed.
	−12	+ 6		+ 6	
	−16	+12		+ 4	
41	+12	0	0	−12	Rate during fibrillation 128 only.
	−44	0	0	+38	
	−30	+15	+15	0	
	−32	0	0	+30	
42	−12	+18	0	+ 6	Heart exposed.
	− 2	+14	+ 4	− 4	
	+10	0	0	−10	Rate during fibrillation 193 only.
43	−48	+28	+12	+ 8	Heart exposed.
	−36	0	0	+20	
44	−18	+ 8	0	+10	Heart exposed.
	−30	+20	+ 2	+ 8	
45	−28	+14	+10	+10	Heart exposed.
	−34	+20		+18	
46	+10	0	0	−10	Rate rise of 55 beats per minute. Heart exposed.
	−30	0	0	+30	
	−40	0	0	+40	
47	− 6	0	0	+ 6	Heart exposed.
	−42	+40		0	
	−12	+ 8		+ 6	
48	−16	0	0	+10	Heart exposed.
49	−10	0	+ 4	+10	
50	−14	0	0	+10	Heart exposed.
51	−18	+10	0	+ 6	Heart exposed.
	−20	0	0	+20	
52	−40	+10	+ 2	+24	Heart exposed.
53	−28	+ 8	+ 2	+14	Heart exposed.

[5] The pressure fell 36 mm. at the onset, rose again 16 mm., ran horizontally, and rose 20 mm. at the offset. Thus it returned to its original level.

the auricular substance. The electrode wires were rubber coated and passed between the layers of the chest wall. Any air which had entered the pleura was withdrawn, the window in the chest wall being closed.

CHANGES IN MEAN ARTERIAL PRESSURE.

The following observations are based upon manometric readings in five dogs and thirty-seven cats.

TABLE II.

Arterial Pressure.

The Effect of Auricular Fibrillation in Dogs.

Dog.	Onset.	After first few seconds.	After second few seconds.	Offset.
CP	+ 9	0	0	−10
CL	−30	0	+8	+20
	−40	+12	0	+12
CK	−44	+34		0
	−82	+36	0	+30
CO	+ 9	0	0	− 9
	−15	+21	−6	0
CN	−30	+16	0	+12
	−28	+22	0	0

a   *b*   *c*
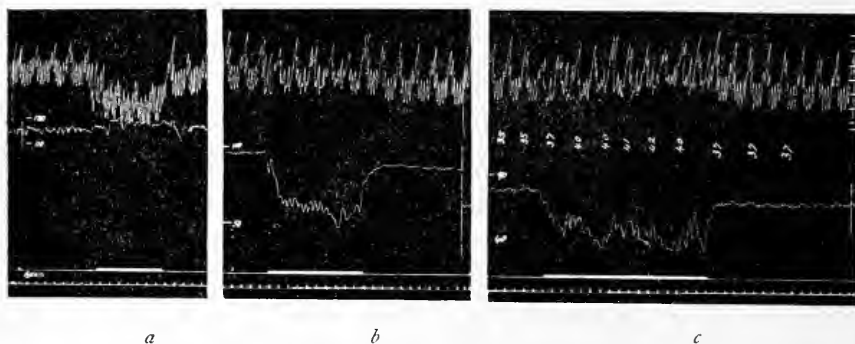
TEXT-FIG. 2, *a*, *b*, and *c*. Three portions of a tracing showing arterial pressure and heart volume curves taken from a series of observations. The first curve (figure 2, *a*) shows a rise of mean arterial pressure at the onset of fibrillation, an increase of cardiac output and a decrease of cardiac volume. The second curve (figure 2, *b*), in which the blood pressure has fallen, shows a deep fall of arterial pressure, a fall of cardiac output, and a slight and progressive increase of cardiac volume. In the third curve (figure 2, *c*), in which the arterial pressure has fallen still lower, a fall of blood pressure occurs at the onset of fibrillation and it is accompanied by a decrease of cardiac output, and by a considerable and progressive increase of cardiac volume. With the rise of pressure in figure 2, *a*, the heart action is far more regular than with the falls of blood pressure in figure 2, *b* and *c*.

The effect of auricular fibrillation, and its accompanying phe-
nomena, is very varied in experiment. At its onset, the mean
arterial pressure may remain unchanged; it may rise at once (text-
figure 2, *a*); but much more commonly there is an immediate fall
(text-figure 1). The greatest rise has been noted in a cat, and
amounted to twenty millimeters of mercury; the greatest fall oc-
curred in a dog, and amounted to eighty-two millimeters of mercury.
The fall which is customary in both cats and dogs is usually
twenty to forty millimeters of mercury. When an immediate
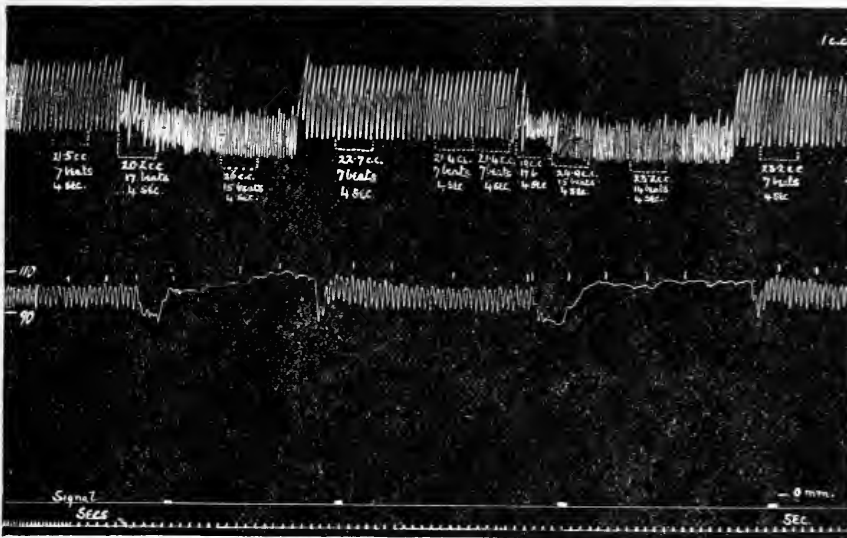
TEXT-FIG. 3. Cat 42. Curves of arterial pressure and heart volume, showing
the effects of auricular fibrillation. The output and number of heart beats per
four seconds are marked from time to time along the upper or cardiometer
curve. The output varies in the same direction as the blood pressure. In the
cardiometer curve, systole is indicated by a downstroke. Note the diminution
of heart volume during the period of fibrillation.

rise occurs, it may be succeeded by a fall of less degree within
a few seconds; when an immediate fall occurs, it is usually
succeeded by a rise of less degree within a few seconds. Thus
the circulation tends to accommodate itself to the altered con-
ditions and this is especially so when there is no initial fall of

pressure.   In most experiments where there is a fall of pressure,—
and these are in the majority,—a quick return towards the previ-
ously recorded pressure is observed, as I have stated; the original

a
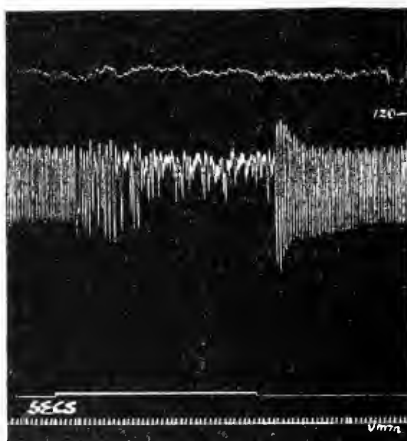
b

TEXT-FIG. 4, *a* and *b*.   Figure 4, *a* (cat 33), gives arterial pressure and intes-
tinal volume curve, showing the effects of faradization of the right auricle.
Figure 4, *b* (dog CP), gives curves of arterial pressure and intestinal volume,
showing the effects of faradization of the auricle.   During the period of fibrilla-
tion the mean blood pressure is raised and the intestinal volume is increased.

pressure may be regained or surpassed (text-figure 3) ; commonly the rise becomes slower and a distinct shoulder is present in the curve (text-figures 1 and 3), which then runs more or less horizontally or rises gradually. The commonest type of arterial curve consequently consists of an abrupt fall, a preliminary and steep rise of about a third or half the extent of the former, and finally a horizontal or a gradually rising curve, the latter spread over a few seconds or a minute. Eventually the pressure lies within five to fifteen millimeters of the original pressure, and when, or shortly after stimulation of the auricle ceases, the pressure returns to normal. This return is abrupt, and often goes beyond the normal limit (text-figure 4, *a*), returning again within a few seconds. If the fibrillation is maintained for five minutes or more, the arterial pressure has usually risen to within five or fifteen millimeters of the original level, though it may remain lower.

Tables I and II give selected figures of the arterial pressure changes in the eighteen cats and five dogs.

CHANGES IN VENOUS PRESSURE.

The venous pressures have been taken from the femoral vein by means of a manometer containing magnesium sulphate in solution (specific gravity, 1,046). The tip of the venous cannula was passed into the femoral vein so that its mouth lay in the iliac vein; and the readings were taken by noting the position of the meniscus in relation to a millimeter scale, and were recorded in writing on the curve at intervals of a few seconds. All experiments in which no movements of the meniscus with respiration were discerned have been discarded.

The changes of venous pressure when the auricle passes into fibrillation are slight. They have been determined in a number of observations upon five cats and two dogs, and the observations permit certain general statements to be made. When the arterial pressure is maintained at the original level, the venous pressure also remains unchanged. A rise of venous pressure is the customary event, for there is usually a fall in arterial tension: and the latter being usually twenty to forty millimeters of mercury, the former generally amounts to five to ten millimeters of magnesium sulphate solution. The arterial and venous pressures move in opposite directions, and this relation is generally maintained not only during the preliminary, but also in the later stage of an observation. Thus,

if the arterial fall is deep and the recovery prompt, the venous pressure after first rising falls again; and when at the offset of fibrillation the arterial pressure reaches its original level, or when it is restored during the fibrillation period, the venous pressure also falls to normal. While these general rules hold good, there are natural exceptions from time to time, for the fluctuations of venous pressure as a result of the change in cardiac mechanism are usually small, and the venous pressure shows variations which are independent of the nature of the heart beat (tables III, IV, and V).

TABLE III.

CAT 47.

Arterial pressure in mm. of mercury.	Venous pressure in mm. of magnesium sulphate.	
82	72–75	
80	72–75	
		Auricles fibrillated.
52	82–92	
52	82–87	
74	77	
80	72	
80	72	
		Normal rhythm restored.
80	72	
78	72	
78	72	
78	70–72	
78	70–72	
		Auricles fibrillated.
60	82	
56	87	
70	92	
78	77	
76	75	
76	75	
75	75	
76	72	
76	77	
		Normal rhythm restored.
78	74	
78	60–72	
78	60–72	
79	60–72	

TABLE IV.
CAT 30.

Arterial pressure in mm. of mercury.	Venous pressure in mm. of magnesium sulphate.	
132	91	
	81–90	
	81–90	
120	80–86	
		Auricles fibrillated.
98	103–104	
	91–96	
	88–96	
104	88–96	
		Normal rhythm restored.
111	71–81	
104	74–81	
		Auricles fibrillated.
81	94–101	
	86–92	
92	82–91	
		Normal rhythm restored.
96	70–76	
98	71–79	
		Auricles fibrillated.
78	88–98	
	86–94	
	85–94	
	88–96	
	86–95	
	90–96	
94	83–92	
		Normal rhythm restored.
111	71–79	
116	71–79	
120	71–78	
		Auricles fibrillated.
84	94–101	
99	86–91	
	84–91	
	91–98	
	91–98	
102	91–96	
	81–91	
		Normal rhythm restored.
120	70–78	
	70–76	
		Auricles fibrillated.
132	61–69	

TABLE IV (Continued).

CAT 30.

Arterial pressure in mm. of mercury.	Venous pressure in mm. of magnesium sulphate.	
90	86–91	
104	81–86	
	81–86	
	86–91	
108	86–91	Normal rhythm restored.
125	66–71	
	61–66	
	61–66	
123	59–63	Auricles fibrillated.
84	76–81	
	79–83	
90	81–86	Normal rhythm restored.
118	61–66	
	59–63	
	59–61	
118	59–61	

TABLE V.

CAT 29.

Arterial pressure in mm. of mercury.	Venous pressure in mm. of magnesium sulphate.	
116	67	
	69	Auricles fibrillated.
118	70	
	75	
114	77	Normal rhythm restored.
110	80	
100	40	Auricles fibrillated.
104	45	
	47	
102	50	Normal rhythm restored.
96	50	

TABLE V (*Continued*).

Arterial pressure in mm of mercury.	Venous pressure in mm. of magnesium sulphate.	
128	43	
	42	
124	39	
		Auricles fibrillated.
118	45	
118	45	
116	45	
		Normal rhythm restored.
118	37	
114	37	
78	33	
78	33	
		Auricles fibrillated.
	CAT 29.	
68	40	
68	32	
68	32	
		Normal rhythm restored.
78	33	
76	33	

TEXT-FIG. 5. Cat 47. A record of arterial and venous pressures and of heart and intestinal volumes, showing the effects of auricular fibrillation. At the time this curve was taken the intestinal record was not working well and the dip in the curve, indicating diminution of intestinal volume, is only just seen.

That the changes in the arterial and venous systems are the direct outcome of altered cardiac mechanism is indicated by the general manner in which the pressures behave. The peripheral circulation is affected passively. This is also shown by records of intestinal volume. Examples of venous readings are given in text-figures 1, 2, *c*, and 5.

CHANGES IN THE INTESTINAL CIRCULATION.

The volume changes in the small intestine were measured in the usual manner by enclosing a loop of the gut in an air-tight box connected to a recorder. The activity of the vasomotor system was checked at the termination of each series of observations by the injection of a suitable dose of adrenalin solution, so as to demonstrate the customary fall of volume with the rise of blood pressure. Observations have been made upon six cats and two dogs from this point of view; they have given uniform results.

The volume curves at the onset of fibrillation have always run parallel with the arterial pressure changes; a fall of arterial pressure is accompanied by a fall of volume (text-figure 4, *a*), and conversely a rise of blood pressure, be it primary or secondary, is accompanied by a rise of intestinal volume (text-figure 4, *b*). The changes in volume at the offset of fibrillation correspond in the same fashion with the changes of arterial pressure.

As might be anticipated, alterations such as occur in the arterial and venous pressures are consequently explained by the altered cardiac mechanism and by this alone. Observations which have been made upon the output of the heart are confirmatory of this conclusion.

CHANGES IN THE VOLUME OF THE HEART.

The mean volume changes of the heart at the onset and offset of fibrillation of the auricles have been estimated by opening the chest, cutting away all but a short sleeve of pericardium, enclosing the whole heart in a glass cardiometer and rendering the mouth of the cardiometer air-tight by tying the sleeve of pericardium firmly over it. The records were taken in twelve cats by means of the recorder designed by Starling[6] for the purpose. The recorder may be calibrated and the excursions are uniform for like changes of volume within the necessary limits.

The volume of output has been calculated by adding together the length of all the downstrokes, representing systoles, over a definite period of time. The

[6] Jerusalem, E., and Starling, E. H., *Jour. Physiol.*, 1910, xl, 286.

excursions yielded by changes of volume of 1 cm. are ascertained at the subsequent calibration. The method gives a fairly accurate expression of output in cubic centimeters while the heart beats regularly, and its accuracy is independent of the variations in excursion consequent upon respiration. It is also, I believe, fairly accurate when the ventricle beats irregularly, though under such circumstances the readings tend to be too high. This is due probably in some part to the inefficiency of certain ventricular beats. While the auricles are fibrillating, a large number of ventricular contractions fail to open the aortic valves; yet it is impossible to avoid a certain excursion in the recording lever as a result of change in the shape of the heart when no blood leaves it, even with the closest fitting cardiometer. Such excursions add to the sum of the calculated output. Consequently in some of the experiments the readings during the fibrillation period have been obviously too high, but the comparison of readings over periods of change of blood pressure has given uniform results. The figures obtained have been regarded relatively rather than absolutely, and treated in this fashion they are of value.

When the blood pressure changes in response to onset or offset of fibrillation, or when it changes during the fibrillation, the output also changes. If there is a fall of pressure there is a fall of output; if there is a rise of pressure there is a rise of output. Examples are given in tables VI and IX and text-figures 2, 3, 5, and 6.
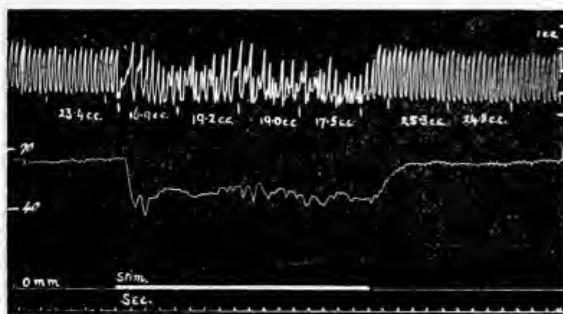
TEXT-FIG. 6. Cat 43. Vagi cut. Arterial pressure and heart volume curves, showing the effects of auricular fibrillation. The heart output and arterial pressure vary in the same directions. There is only a slight decrease in the mean size of the heart.

Mean Volume Changes.—When the auricles pass into fibrillation, the heart demonstrates a change in mean volume, of which the direction is practically constant. The volume decreases.[7] This is

[7] I shall refer briefly to certain exceptions to this rule in my concluding remarks.

TABLE VI.

Cat.	Before fibrillation			After onset				A few seconds later			After offset		
	Blood pressure (mean).	Heart rate.	Output per 4 sec. in c.c.	Blood pressure (mean).	Heart rate.[8]	Output per 4 sec. in c.c.	Volume change in c.c.	Blood pressure (mean).	Heart rate.[8]	Output per 4 sec. in c.c.	Blood pressure (mean).	Heart rate.	Output per 4 sec. in c.c.
42	98	105	21.5	87	255	20.2	−1.4	108	225	26.0	100	105	22.7
	98	105	21.4	87	255	19.0	−1.5	104	210	24.9	104	105	23.2
	Left vagus cut.												
	104	172	20.9	82	270	17.1	−0.3	100	262	21.7	98	150	21.7
43	82	135	24.8	60	165	14.8	−1.3	60	165	15.0	84	135	26.2
	Right vagus cut.												
	68	180	19.8	46	300	15.0	0	47	292	15.0	67	180	23.0
	Left vagus cut.												
	65	172	23.4	46	255	16.9	−0.4	50	270	19.0	64	180	24.8
44	82	169	29.4	63	285	16.0	−1.2	62	277	16.0	82	177	28.0
	73	170	15.3	34	258	6.1	+1.0	64	255	11.8	75	168	17.2
47	82	202	40.7	57	365	30.3	−1.4	76	250	39.1	78	200	39.8
	78	195	38.7	58	360	22.7	−1.4	75	250	37.7	78	200	40.6
49	67	186	25.5	58	300	18.0	−0.4	55	285		66	177	25.2[9]
	All cardiac nerves divided.												
	60	163	22.4	49	270	15.2	0			19.4	63	157	23.4

[8] Heart rates are calculated from cardiometer curves; approximate readings.

[9] Fibrillation lasted only a short while.

indeed obvious from mere inspection of the organ. The decrease
in size is seen whether the arterial pressure rises (text-figures 2, *a*,
and 3), falls (text-figures 5 and 6), or remains stationary. It is
due entirely to change in the size of the ventricles. The auricles,
it is true, are included in the cardiometer, but they pass into a posi-
tion of diastole, or increased mean volume, when fibrillation begins.
Examples of the mean volume change will be found in tables VI and
IX, and in the figures to which reference has been made.

SUMMARY OF PREVIOUS OBSERVATIONS.

As far as I have recorded my observations, they show that
fibrillation produces changes in arterial pressure, which consist of
certain falls and certain rises of pressure. The venous pressure
moves in the opposite direction from the arterial pressure. If we
compare increase and decrease of arterial pressure with increase
and decrease of intestinal volume, it may be said that they change in
the same direction, as does also the cardiac output. We may con-
clude, therefore, that the changes in arterial pressure are due solely
to the change in the mechanism of the heart beat and we may seek
the cause of all the circulatory pressure changes in this organ.[10]

We have to consider the cause of the usual steep fall of arterial
pressure at the onset of fibrillation. We have to determine the
cause of the partial or complete recovery in certain instances, the
cause of the variation in the reaction in different experiments, and
the cause of the fluctuation of pressure during fibrillation in a given
experiment. We have also to seek the reason for the change of
cardiac volume.

It has become more and more apparent, during the course of the
experiments, that the explanation of most of these phenomena lies
in the acceleration of the heart's rate, though it has not been
altogether easy of proof. The effects of auricular fibrillation and
of simple tachycardias, provoked by applying regular induction
shocks to the right auricle, have been compared.

[10] The changes are not affected by section of the vagi or sympathetics.

DEGREE OF VENTRICULAR ACCELERATION WHEN THE AURICLES
FIBRILLATE, AND THE EFFECT OF REGULAR ACCELERATION
OF SIMILAR EXTENT.

A number of figures, giving the ventricular rates before and after
the onset of fibrillation, will be found in tables VI and IX; these
rates were calculated from cardiometer curves. In blood pressure
tracings the rate of the ventricle cannot often be estimated during
the period of fibrillation, because the irregularity of the ventricle is
so gross and because usually so many beats of the ventricle fail to
affect the arterial pressure. The curves of heart volume give more
accurate readings, and readings which are approximately correct.
But at the present time, that the true grade of acceleration may be
appreciated, I give the following figures (table VII), taken from
electrocardiographic curves in a separate series of experiments.
The conditions of the animals in these experiments were similar to
those described in the present series.

TABLE VII.

	Before onset of fibrillation.	After onset of fibrillation.
Dogs	95	185
	170	230
	157	237
	183	330
	149	255
	102	205
	117	198
	165	240
	160	270
	185	283
Cats	151	304
	192	330

Other figures are given in the sequel.

The acceleration of the ventricle, when the auricles pass into
fibrillation, is from 50 to 100 per cent. under normal experimental
conditions. The rate of the ventricle during the period of fibrilla-
tion varies in dogs and cats approximately between 180 to 330 beats
per minute.

In several experiments, a simple manometric comparison was
made between the effects of auricular fibrillation and regular ac-

celeration. The mercurial manometer was employed, and after electrodes had been fastened to the right auricle the chest was closed. Examples of the results are seen in table VIII. The

TABLE VIII.

CAT 52.

	Ventricular rate rises from	Blood pressure changes from
Fibrillation	207 to ——	107 to 86
Tachycardia	184 to 190	102 to 104
Tachycardia	176 to 285	113 to 109
Tachycardia	176 to 288	113 to 107
Tachycardia	178 to 242	112 to 112
Tachycardia	178 to 236	113 to 115
Tachycardia	177 to 208	111 to 113
Tachycardia	176 to 210	112 to 113
Tachycardia	176 to 236	112 to 113
Tachycardia	175 to 256	112 to 110
Tachycardia	180 to 286	112 to 103
Tachycardia	174 to 256	110 to 110
Tachycardia	176 to 258	110 to 108
Tachycardia	171 to 268	111 to 103
Tachycardia	174 to 276	109 to 93
Tachycardia	172 to 310	107 to 73
Fibrillation	174 to ——	109 to 79

CAT 53.

Tachycardia	236 to 395	90 to 51
Tachycardia	228 to 364	89 to 66
Fibrillation	230 to ——	88 to 62
Tachycardia	186 to 338	77 to 43
Tachycardia	188 to 305	77 to 47
Tachycardia	200 to 258	80 to 74
Tachycardia	195 to 246	81 to 78
Tachycardia	190 to 236	82 to 81
Tachycardia	183 to 236	82 to 81
Tachycardia	192 to 236	83 to 81
Tachycardia	192 to 204	82 to 82

ventricular rate during the periods of simple tachycardia could be estimated readily from the arterial curves and signal of stimulation. The estimation of rate during the periods of fibrillation was not possible. It will be seen that considerable acceleration of the ventricle (to 242, 256) may occur without change of arterial pressure, or

that such increase of rate may be accompanied by a slight rise or slight fall of arterial pressure. It will also be seen that, as higher rates are reached, small falls of pressure ensue and that eventually, as the rate increases, the fall becomes greater, until when the heart rate rises to 300 or more per minute, falls result which are equivalent to those obtained in fibrillation. These rates are of the degree known to occur when the auricles are fibrillating. The actual figures naturally vary very much from experiment to experiment, and an absolute comparison is by no means easy. It is difficult to obtain comparable falls with simple and with irregular acceleration, for the degree of fall varies with so many factors; for example, with the original height of venous and arterial blood pressure and with the original heart rate. The chief defect of the method now described lies in the impossibility on most occasions of ascertaining the ventricular rate during the period of fibrillation. Other examples, from experiments in which the chest was open, and in which the rates were calculated from cardiometer curves, are given in table IX. These figures confirm the conclusion that the rate is

TABLE IX.
Vagi and Sympathetics Cut.

Cat 50.

	Ventricular rate rises from	Blood pressure falls from	Heart decreases in size by approximately	Output per 4 secs. in c.c. decreased from
Fibrillation	200 to 283[11]	86 to 72	1.3 c.c.	
Fibrillation	192 to 275[11]	84 to 72	1.3 c.c.	
Fibrillation	174 to 230[11]	80 to 66	1.4 c.c.	25.2 to 21.0
Tachycardia	170 to 190	71 to 71	0.25 c.c.	22.6 to 21.2
Tachycardia	172 to 301	73 to 73	0.33 c.c.	23.9 to 22.8
Tachycardia	181 to 204	60 to 59	0.25 c.c.	18.7 to 14.9
Tachycardia	190 to 263	55 to 49	0.5 c.c.	17.8 to 10.8

Cat 51.

Sympathetics Cut.

Fibrillation	156 to 205[11]	58 to 48	1.4 c.c.	23.0 to 21.2
Tachycardia	155 to 195	58 to 57	1.0 c.c.	
Tachycardia	153 to 185	57 to 56	0.8 c.c.	24.2 to 23.1
Tachycardia	150 to 223	59 to 54	1.4 c.c.	23.3 to 17.5
Tachycardia	150 to 190	60 to 59	1.0 c.c.	
Fibrillation	140 to 216[11]	58 to 47	1.0 c.c.	
Fibrillation	139 to 196[11]	56 to 42	1.0 c.c.	

[11] These figures, taken from counts in the cardiometer curve, are approximate.

a predominant factor in producing the usual fall of blood pressure, though they indicate that acceleration, when the ventricular action is regular, is less profound in its effects than is acceleration when the ventricular regularity is disturbed. The last named experiments were performed for the sake of heart volume curves, rather than for the rate readings.

The question has been approached in a more direct manner in further experiments. In these, animals in which the chest wall was subsequently closed have been utilized. In two experiments the blood pressures were recorded with the mercurial manometer, and the rates were calculated from simultaneous electrocardiograms. While the blood pressure was running steadily, a faradic current or repeated induction shocks at varying rates were passed into the auricle through the chest wall by means of the specially protected electrodes. When a pressure fall of uniform extent was obtained after several faradic stimulations, a fall of similar amount, as far as this was possible, was obtained with regular induction shocks; this was accomplished by varying their rate of incidence. The experiment was then repeated, and at the same time electrocardiograms
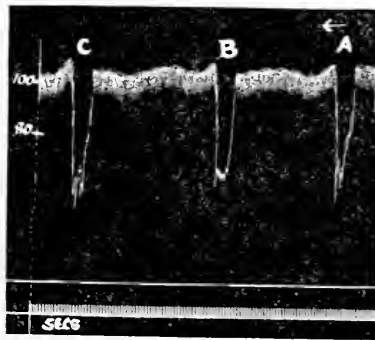
Text-Fig. 7. Cat 67. Unlike the remainder of the figures, this blood pressure curve reads from right to left. It shows a fall of blood pressure obtained with (*A*) faradization of the auricle, (*B*) regular acceleration of the auricle, and (*C*) faradization of the auricle. The heart rates corresponding with these three curves were 216, 225, and 231 respectively.

were taken from the right fore limb and left hind limb. Such experiments are not easy, because, apart from variations in the general

line of blood pressure, similar curves of blood pressure during fibrillation are not often obtainable : and it is necessary that the comparison should be made in the shortest possible time, so that the two curves lie close together.   Text-figure 7 is an example of such an experiment. and selected figures are given in table X.   The read-

TABLE X.

		Blood pressure falls from	Heart rate rises from	
I	Fibrillation	108 to 94 = 14	188 to 216	
	Tachycardia	112 to 96 = 16	185 to 249	
II	Fibrillation	120 to 100 = 20	180 to 220	
	Tachycardia	126 to 90 = 36	179 to 261	
	Tachycardia	112 to 87 = 25	180 to 249	
III	Fibrillation	86 to 68 = 18	150 to 207	
	Tachycardia	104 to 85 = 19	154 to 222	
IV	Fibrillation	102 to 68 = 34	145 to 216	(Figure 7,
	Tachycardia	100 to 65 = 35	147 to 225	*A, B,* and *C.*)
	Fibrillation	100 to 62 = 38	147 to 231	

ings confirm the previous observations.   Regular and irregular accelerations of similar rate produce approximately equal falls of pressure, but the irregular acceleration is almost always a little more profound in its effects.   That is to say, if equal falls of pressure are obtained, it is subsequently found that the rate during the period of regular acceleration slightly exceeds that of the period of fibrillation.

When the auricles fibrillate, a number of heart beats fail to affect the arterial curve and are entirely lost.   The series of experiments was therefore extended, and arterial curves were taken from five animals with Hürthle's manometer, the two records, arterial and electrocardiographic, lying on the same plate.   Repeated observations are required before curves are secured in which systolic and diastolic readings are alike and in which a comparison is valid. Nevertheless, out of a large number of such curves, some may be chosen from which the required data are obtainable ; the readings conform to those obtained in other ways.   Two observations are chosen for illustrative purposes ; in selecting them attention has been paid to the form of the arterial curve during the period of fibrilla-

tion. In figure 1, *a* and *b* (plate 43), there are two falls of blood pressure. The original systolic and diastolic pressures are the same in both curves during the interval of depression; the average diastolic pressure is somewhat lower in the curve which shows fibrillation. The average ventricular rate is 300 for the fibrillation curve, and 306 for the curve which shows regular acceleration. Thus the falls of pressure for similar rates are approximately equal, though again the fibrillation has a somewhat more profound effect. Figure 2, *a* and *b* (plate 43), are from a similar experiment. The original pressures in each curve are almost the same. The initial fall is somewhat greater in the fibrillation curve; eventually the blood pressure rises above that shown at a similar phase of figure 2, *a,* and once more falls below it. The respective rates for figure 2, *a* and *b,* are 315 and 328.

If we continue to consider the cause of the usual fall of arterial pressure, the part played by the average rate of heart beat at such times seems clear. It appears to be the all important factor. There is, however, another conceivable cause of the fall of pressure. It has been recently emphasized by Gesell[12] as a reason for a pressure fall in auricular fibrillation. Gesell produced complete heart-block experimentally; thus he dealt with hearts in which the ventricles beat at uniform rates; he then experimented with the auricles, eliminating their systoles by inducing fibrillation in them. In this way he produced falls of blood pressure of 10 mm. of mercury. His conclusion, from this and other experiments, that the auricles aid in ventricular filling to an extent which may not be neglected, cannot be questioned; but at the same time, the absence of auricular filling cannot be considered a serious factor in the production of the falls of pressure with which we now deal. Such a possibility requires discussion, because in the comparison which has been instituted in the present series of experiments this factor is neglected. In those instances in which regular acceleration is induced and in which it is of a sufficiently high grade to produce large falls of blood pressure, auricular filling does not occur. The auricles are as much out of action as they are when they fibrillate, for each auricular contraction falls with the preceding ventricular systole; this is evident in the electrocardiograms; *P* falls with the preceding *T* (figure 2, *a*). I draw attention especially to this fact, because the comparison between the regular and irregular acceleration is more perfect. The question arises as to what extent the absence of auricular filling influences the result. Gesell produced falls of pressure of only small extent, about 10 mm. of mercury. It must be remembered that in these experiments each ventricular cycle was accompanied by four or five auricular cycles at the time when fibrillation of the auricles was induced. The ventricle fills, under ordinary circumstances, chiefly during the early and late phases of diastole. The information which we require is the relation of

[12] Gesell, R. A., *Am. Jour. Physiol.,* 1911, xxix, 32.

the amount of early filling by static pressure to the late or forcible auricular filling. When the ventricle beats slowly, the filling during mid-diastole is slow, unless, as in Gesell's experiments, there is additional or forced feeding as a result of supernumerary auricular contractions. Ten mm. of mercury, therefore, are probably too much to allow as the amount of the fall which is attributable to the auricular factor. That the auricular factor is an unimportant one is clearly evidenced by the varying effect which fibrillation of the auricles has upon arterial pressure. In place of a fall, the blood pressure may remain unaltered; it may actually rise. If in figure 3, *a* (plate 44), the beats marked by asterisks are compared, the second is seen to succeed an auricular contraction. The two beats are of almost the same values; the diastolic pressures are equal, the systolic pressure of the second beat exceeds that of the first by less than 7 mm. of mercury. The difference is fully accounted for by the difference in lengths of preceding pauses; these are 8.6 and 9.4 thirtieths respectively. The filling which precedes the two contractions seems to have been equally rapid. The absence of auricular filling when the auricles fibrillate seems to be almost if not quite compensated for by increased venous pressure, when there is a fall of arterial pressure.

The degree of acceleration not only accounts, I believe, almost entirely for the usual steep fall, but accounts completely for the variations in the amount of fall from time to time, and also for the fluctuations of pressure which are seen during the course of a single observation. Comparisons are of most value under the last named circumstance. When the ventricle beats its fastest, a number of contractions produce no arterial pulsation. The shortest cycles of figure 3, *a* and *b*, correspond to the steepest falls of pressure and to those portions of the curve at which no arterial pulsations are visible. After a careful examination of the curves in my possession I find that there is no exception to the rule which these figures illustrate. If previous events are taken into consideration, each rise and each fall of pressure are fully accounted for by the lengths of the cycles found to correspond to it. That the curve of rate of fall or of rise should not be absolutely parallel to the curve of lengths of pauses is natural, for the effect of a longer or shorter pause is not confined to the immediately succeeding cycle.[13] This is especially the case where the initial fall and terminal rise are concerned; for over these periods the supply of blood to the heart does

[13] Where there is an abortive contraction, as in figure 3, *b* (marked with asterisks), the beat which follows has a greater effect on arterial pressure than may be accounted for by the previous pause; this evidently results from some of the blood of the previous diastole being carried over for one heart cycle.

not immediately meet the requirements of the particular pauses in question; the supply may be excessive, or it may be scanty.

A short pause is equivalent to a fleeting acceleration; a long pause is equivalent to a fleeting retardation. Moreover, a short pause counts more heavily than a relatively long one; the study of regular acceleration teaches that great acceleration produces effects out of proportion to the increase of rate. If over two equal periods the rate is the same, but over one the heart action is regular while over the other long and short pauses are mixed, the effect is more profound over the latter. Whenever the blood pressure rises at the onset of fibrillation, or wherever it rises above the original point during the progress of fibrillation, the action of the ventricle is more regular, both in the incidence of the excursions and the amplitude of the beats, in arterial and cardiometer curves (text-figures 2, *a,* and 3); it is also slower. The rates corresponding to the four rises of pressure tabulated in table I were 102, 128, 193, and 255.[14] Where the ventricle beats fast, the arterial pulse and cardiometer curves are very irregular (text-figures 5 and 6), for many of the contractions of the ventricle fail to raise the aortic valves. The initial falls of pressure in text-figure 3 are marked in the cardiometer curve by very irregular heart action; the upstrokes of diastole are notched by the weak contractions which are abortive. The periods of raised pressure in the same figure correspond to more regular heart action. Contrast with this the gross irregularity of text-figure 6; it is maintained throughout, and the pressure is low throughout. When it is remembered that such gross irregularity signifies rapid action, the reason of the fall and its maintenance is more obvious. The same point is illustrated by the falls of text-figure 2, *b* and *c.* Where the pulse irregularity is great, and beats are dropped, the pressure falls steeply; where the action is more regular the pressure rises; and where beats are dropped, as we have seen, the pauses which precede them are curtailed.

Thus the fluctuations of arterial pressure are explained by a detailed consideration of heart rate. Falls are due to excessive rapidity, rises to less rapid action; a rise above the initial pressure is comparable to the occasional small rises which result from simple acceleration. Briefly, the changes in the peripheral circulation are

[14] In this instance the original rate was 200.

most serious when the acceleration is greatest.   That is a conclusion which is fully borne out by clinical experience.   When fibrillation is present, the rate of ventricular action is one of the most important indications of the gravity of the condition as a whole.

The initial fall is usually the deepest, as I have stated, though this is not invariably the case; but it is deepest in a sufficient percentage of cases to place its occurrence beyond the possibility of coincidence. The most rapid ventricular action is also found at the onset of the disturbance and accounts for it. The reason why the ventricle beats more rapidly when fibrillation begins is probably that at the onset of fibrillation the tissues which transmit the impulse from auricle to ventricle are usually unfatigued. When after a fall the initial pressure is recovered and fibrillation persists, the recovery may be assigned to lessened conduction power between auricles and ventricles. The recovery is probably due also in a measure to increased venous pressure. The falls which accompany acceleration are the result of curtailment of the diastolic periods; a heightened venous pressure, by promoting the filling, will tend to compensate for it.

The final rise at the termination of the fibrillation needs no detailed explanation; it is due, as is the frequent overriding of the initial pressure, to the transference of the obstructed blood from the venous to the arterial system.

CAUSE OF THE MEAN VOLUME CHANGE.

It has been stated that when the auricles pass into fibrillation, the heart volume decreases. A similar reaction is found when the heart rate shows regular acceleration (table IX and text-figure 8). Up to a certain point the greater the acceleration, the greater is the decrease of volume. It may be, as in table IX, cat 51, that if regular and irregular accelerations are approximately equal in degree, the volume decrease is of approximately equal amounts. On the other hand, and perhaps more commonly, the regular acceleration may be accompanied by a relatively smaller decrease (table IX, cat 50).

The chief factor in producing diminution of heart capacity when the auricles fibrillate is the same as that which produces it when the acceleration is regular. The diastolic intervals are curtailed; it is the diastolic volume which shows the chief reaction; the systolic volume also suffers, though to a less extent. The heart is smaller at all phases of its beat. But the decrease in heart volume is independent of the velocity of flow through it. The flow is usually decreased when there is a fall of pressure, but it may be increased when there is a rise above the initial pressure (text-figure 3). Thus, although the diastolic intervals are decreased, the blood flow into the heart may be even in excess of the initial flow. Under these circumstances the average rate of inflow must have increased. The reason for such an increase is not to be found in an increased venous pressure; it must consequently be due to a lowering of mean diastolic ventricular pressure. There seems, therefore, to be no alteration of the ventricular function which is spoken of as " tone." The decrease of heart volume appears to result

from more purely mechanical causes; shortening of the diastolic periods as a result of acceleration is sufficient alone to account for it. Section of all the cardiac nerves does not influence the reaction.

The decrease of mean heart volume is the almost constant reaction of the normal heart; but in the human subject the onset of auricular fibrillation is often accompanied by obvious increase of volume. I have seen dilatation on a few occasions in the present series of experiments. The actual cause of this unusual reaction has been difficult to ascertain, but it may have been due, as probably is
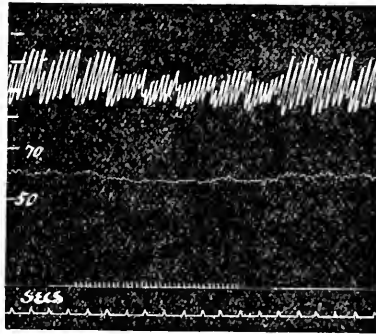
TEXT-FIG. 8. Cat 50. Arterial pressure and heart volume curves, showing the effects of stimulating the auricle with a succession of regular induction shocks. The blood pressure is lowered and the heart volume and output are decreased.

the reaction of the human heart, to nutritional changes in the ventricular muscle. A weak or failing muscle will not necessarily react in the same manner as does fresh and vigorous tissue.

There is perhaps no quality of heart muscle which it is more difficult to estimate at a given moment than its state of exhaustion, and I write with hesitancy of the relation of dilatation to such a quality at the onset of fibrillation. More observations are required before any views can be exposed with confidence. Where it occurs, the dilatation of the ventricles at the onset of fibrillation is usually seen towards the end of an experiment. It is usually associated with relatively low blood pressure. This will be evident from an examination of table VI; dilatation of the heart or unchanged volume accompany initially low arterial tensions.

On one occasion a series of curves was obtained from an animal, in which a complete transition was seen from decreasing to increasing volume. Three curves from this series are shown in text-figure 2. The blood pressure, which falls steadily throughout the whole series, rises in the first curve when fibrillation begins; it falls in the second and third curves. The volume decreases by several cubic centimeters in the first curve; it shows slight progressive increase in the second, and considerable and progressive increase in the third. The explanation of this series of volume changes seems to be that from first to last there was a steady exhaustion of the muscle, so that while at first, being vigorous, it reacted in the usual fashion, maintaining its tone, toward the end the increase of rate was speedily followed by loss of tone.

SUMMARY AND CONCLUSIONS.

When the auricles fibrillate, the following effects are observed.

1. The arterial blood pressure may rise, fall, or remain stationary. Usually it falls. If it falls, it generally rises again towards or to the initial pressure.

2. The venous pressure changes are the reverse of the arterial.

3. The intestinal volume and the cardiac output changes are in the same direction as those of arterial blood pressure.

4. From these observations it may be concluded that the peripheral circulatory effects are purely passive.

5. The volume of the heart decreases except in instances where there is reason to believe that the circulation is failing.

All the changes described in the foregoing paragraphs, and also the variations in blood pressure reactions which occur from time to time, are attributable to alterations in the rate of ventricular contraction. Similar, though perhaps less profound changes, are seen when the heart rate accelerates in like degree in response to regular induction shocks.[15]

EXPLANATION OF PLATES.

PLATE 43.

FIG. 1, *a* and *b*. Cat 64. Hürthle manometer curves from the carotid, and electrocardiograms. In *a* the auricle was faradized. In *b* regular induction shocks were employed. The falls of pressure are equal; the respective rates of ventricular action are 300 and 305. The time marker is in thirtieths of a second.

FIG. 2, *a* and *b*. Cat 65. Similar curves from another animal; *a* = stimulation with regular induction shocks at a rate of 328 per minute; *b* = faradization; rate of ventricle 315 per minute. The falls of pressure are almost equal.

PLATE 44.

FIG. 3, *a* and *b*. Cat 67. Two electrocardiograms and two Hürthle curves; *a* shows fluctuations of arterial pressure and the return to the normal rhythm at the very end of the curve. The fluctuations of pressure were due to variations in heart rate. The measurements of the beats are expressed in thirtieths of a second. *b* shows the recovery of arterial pressure towards the end of a period of fibrillation, and its cause,—decrease of heart rate.

[15] This conclusion applies only to induction shocks applied to the auricle; the effect of similar stimulation of the ventricle is far more profound. Stimulation of the auricle seems to result in contractions of the ventricle, which are the most efficacious.

FIG. 1

FIG. 2.

FIG. 3.

(Aus der kardiographischen Abteilung der University College Hospital
Medical School in London.)
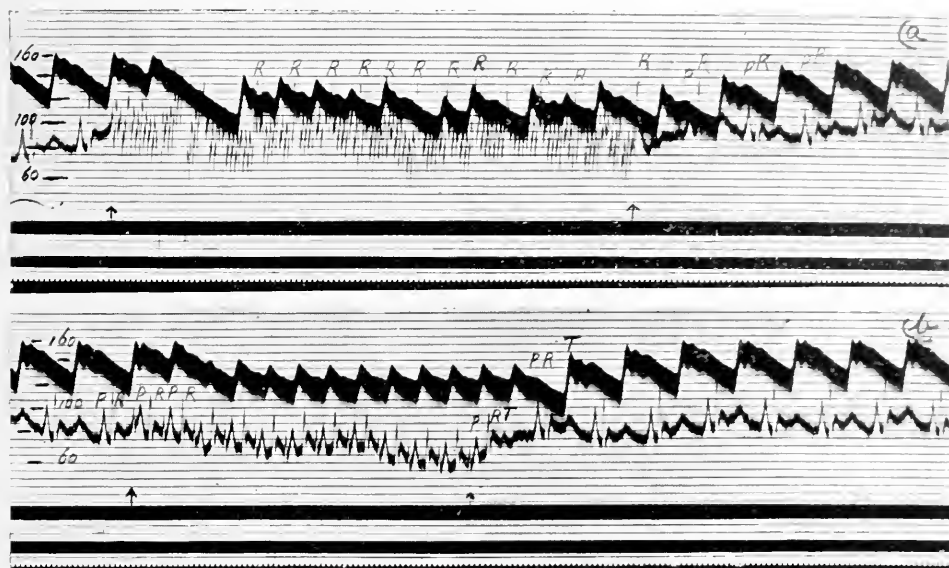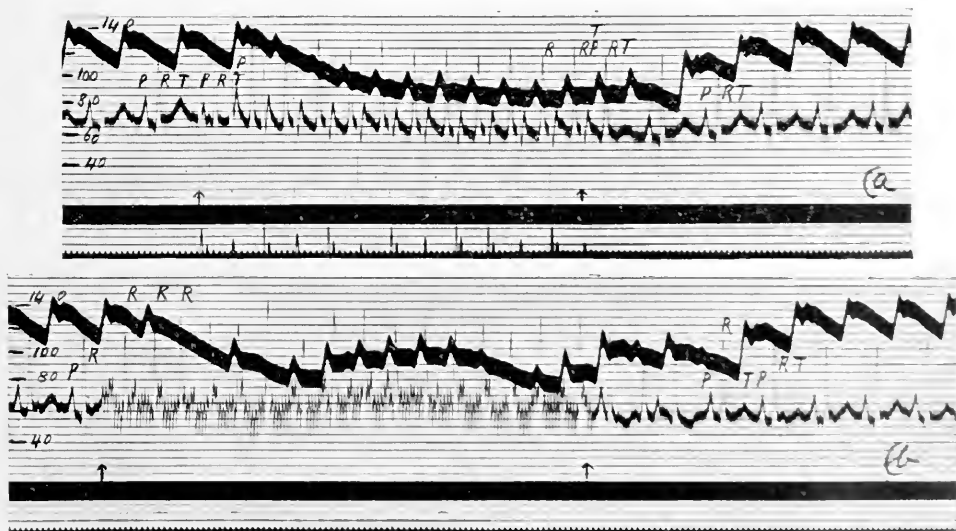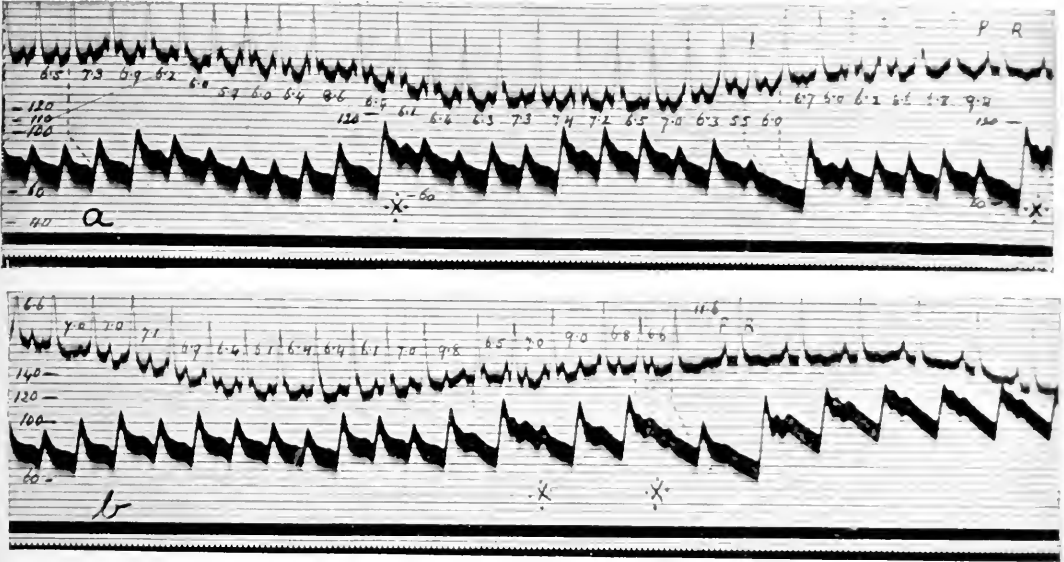
Der Einfluss der Vagi
auf die automatisch schlagende Kammer
(auf den idio-ventrikulären Rhythmus).

Von

Dr. **Johann v. Ángyán** in Budapest.

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(Mit 13 Textfiguren.)

Dass die Vagi einen direkten Einfluss auf die Ventrikeltätigkeit
des Säugetierherzens haben, war schon durch Experimente von
Bayliss und Starling[1]) festgestellt. Diese Autoren zeigten, dass
im Herzen, welches sich in umgekehrter Schlagfolge kontrahiert,
d. h. wo die Vorhöfe der Kammerkontraktion folgen, die Vagus-
reizung einen inhibitorischen Effekt auszuüben vermag. Jedoch wie
Hering[2]) dies auseinandersetzt, da die Autoren sich der Methode
bedient haben, durch elektrische Reizung der Kammer, diesen und
durch Rückläufigkeit auch den Vorhöfen einen künstlichen Rhythmus
aufzuzwingen, ist es nicht klar, ob die Schlagumkehr eine natürliche
oder künstliche war. Im letzteren Falle[3]) würden die Versuche darauf
hinweisen, dass die Anspruchsfähigkeit der Kammer bei Vagusreizung
sich vermindern kann, nicht aber dass die Reizerzeugung in der
Kammer durch den Vagus beeinflusst werden könnte.

Die Frage des Vaguseinflusses auf die ventrikuläre Reizerzeugung
ist viel klarer demonstriert durch die graphisch registrierten Be-

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1) Bayliss and Starling, On some points in the innervation of the
mammalian heart. Journ. of Physiol. vol. 13 p. 407—418. 1892.

2) Hering, Über die unmittelbare Wirkung des Accelerans und Vagus
auf automatisch schlagende Abschnitte des Säugetierherzens. Arch. f. d. ges.
Physiol. Bd. 108 S. 281—299. 1905.

3) Es ist wahrscheinlich, dass Bayliss und Starling über eine durch
artifizielle Reizung entstandene umgekehrte Schlagfolge berichten.

1

obachtungen Rihl's[1]) und Lewis'[2]). Rihl vergiftete seine Tiere
mit Digitalis, Lewis unterband die Äste der Koronararterie. Beide
Autoren erhielten spontane Tachykardien ventrikulären Ursprungs.
In Rihl's Experimenten kontrahierten sich Vorhof und Kammer un-
abhängig, und die Vagusreizung verursachte Kontraktionsstillstand;
darauf folgte Rückkehr zum ursprünglichen Rhythmus. In Lewis'[2])
Experimenten beantworteten die Vorhöfe die Ventrikelschläge, und
die Vagusreizung verursachte entweder nur Vorhofsstillstand oder
aber in 40 % aller Beobachtungen Kontraktionsstillstand im ganzen
Herzen mit nachträglicher Wiederherstellung des normalen Rhythmus.

So stände also sicher, dass der Vagus in einem grossen Prozent-
satz der untersuchten Tiere einen direkten Einfluss auf die Reiz-
erzeugung in der Kammer hatte. All die oben genannten Autoren
benutzten Hunde bei ihren Versuchen.

Die hier vorliegenden Beobachtungen wurden von einem noch
spezielleren Gesichtspunkte aus unternommen. Der Vagus möge
wohl die spontane Reizerzeugung in der Kammer beeinflussen, wenn
die Reizerzeugung von einer der beschriebenen Art ist, nämlich eine
durch Irritation entstandene; aber es folgt daraus noch nicht not-
wendig, dass sein Einfluss auch auf den automatischen Rhythmus
(idio-ventrikulären-Rhythmus) der dissoziierten Kammer derselbe
sei. Es ist notwendig, diese beiden Formen der Reizerzeugung von-
einander zu unterscheiden, und es ist möglich und sogar wahrschein-
lich, dass bei beiden wesentlich verschiedene chemische Prozesse im
Herzmuskel vorliegen. Fasst man diese Möglichkeit ins Auge, so
muss jede Form für sich untersucht werden.

Die Kenntnis vom Verhalten der Kammerautomatie ist von be-
sonderer Wichtigkeit wegen ihrer Beziehung zum klinischen Herz-
block und den Anfällen, welche diesen Zustand so oft begleiten.

Die Ventrikelautomatie wurde schon von einer Anzahl von
Autoren nach dieser Richtung hin untersucht, deren Beobachtungen
hier kurz zusammengefasst werden sollen.

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1) Rihl, Über Vaguswirkung auf die automatisch schlagenden Kammern
des Säugetierherzens. Arch. f. d. ges. Physiol. Bd. 114 S. 545—552. 1906.
2) Lewis, The experimental production of paroxysmal tachycardia and
the effects of ligation of the coronary arteries. Heart vol. 1 p. 98—137.
1909—1910.

Erlanger[1]) hat an Hunden bei durch Anlegung seiner Klemme verursachtem kompletter Herzblock gefunden, dass die Reizung der Vagi „keinen oder höchstens einen unbedeutenden Einfluss auf die Kammertätigkeit ausübt". Hering erzeugte bei einem Kaninchen durch Abschnürung der atrio-ventrikulären Grenze mit einer Schnur Herzblock. Während dem nach Entfernung der Schnur weiter fortbestehenden Herzblock erzeugte die Reizung des rechten oder linken Vagus eine sehr bedeutende Verlangsamung der Ventrikeltätigkeit. Rihl experimentierte an Hunden und glaubt, dass nach Bündeldestruktion die Vagusreizung in erheblicher Weise die Kammerschlagzahl modifiziert. Rihl gibt zwei Kurven, in welchen auch die Vorhöfe verzeichnet sind. In beiden Fällen liegt Dissoziation vor, aber in einem war die Kammertätigkeit irregulär, und im anderen waren ventrikuläre Extrasystolen von längeren Pausen gefolgt als gewöhnlich. Rothberger und Winterberg[2]) hatten Hunde mit Digitalis vergiftet und so die Dissoziation erzeugt. In ihren Experimenten konnten sie niemals finden, dass Vagusreizung die Schlagfolge der Kammerkontraktionen beeinflusst. Kahn[3]) hat nach Bündeldestruktion mit Erlanger's Klemme die Vagi inaktiv gefunden. Erlanger hatte weitere Untersuchungen gemacht und konnte Rihl's Beobachtungen nicht bestätigen. Er schliesst wieder, dass der Vagus keinen oder einen unbedeutenden Einfluss auf die automatische Aktion der Ventrikel hat.

Während unsere Experimente schon im Gange waren, lasen wir eine Mitteilung von Fredericq[4]), in welcher er beweisend zeigt, dass im Falle das Bündel zwar komprimiert, aber nicht destruiert ist, bei der kompletten Dissoziation zugleich eine inhibitorische Verangsamung der Kammerschlagfolge auf Vagusreizung bestehen kann; wenn die Kompression eine stärkere ist, geht die Inhibition verloren.

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1) Erlanger, Journ. exper. Méd. vol. 8. 1906. — Erlanger, Über den Grad der Vaguswirkung auf die Kammern des Hundeherzens. Arch. f. d. ges. Physiol. Bd. 127 S. 77—98. 1909.

2) Rothberger und Winterberg, Über scheinbare Vaguslähmung usw. Arch. f. d. ges. Physiol. Bd. 128 S. 499—510. 1909.

3) Kahn, Elektrokardiogrammstudien. Arch. f. d. ges. Physiol. Bd. 111 S. 634. 1911.

4) Fredericq, Dissociation par compression graduée des voies motrices et arrestatrices contenues dans le faisceau de His. Arch. intern. de Physiol. t. 11 p. 405—417. 1912.

Es erschien uns, dass die Frage des Vaguseinflusses auf das automatische Kammerzentrum eine weitere und eingehendere Untersuchung verlangt, und wir dachten für diesen Zweck den durch Asphyxie verursachten kompletten Herzblock zu benutzen, in welchem, obwohl die funktionelle Kontinuität die muskuläre Reizleitung zwischen Vorhof und Kammer vollständig aufgehoben ist, die Vagusausbreitung im Herzen anatomisch und offenbar auch funktionell intakt ist.

Methodik.

Die Experimente haben zu ihrer Grundlage die Untersuchungen von Lewis und Mathison[1]), die gefunden hatten, dass alle Stadien von Herzblock bei der Katze durch Asphyxie erzeugt werden können. Aus dem Stadium des kompletten Herzblocks kehrt das Herz manchmal nach Wiederherstellung der künstlichen Atmung nicht mehr zum normalen Rhythmus zurück. Wir benutzten etwa zwölf Tiere zur Untersuchung und beobachteten eine Erholung aus komplettem Herzblock nach der Asphyxie bei acht Tieren. Auf diesen acht Experimenten beruhen unsere Schlussfolgerungen. Die Tiere waren anästhetisiert mit Urethan und Äther; die grossen Gefässe am Halse wurden nach Unterbindung durchgeschnitten, ebenso die Vagi und Sympathici. Das Halsmark wurde in der Höhe des Atlas durchtrennt und künstliche Atmung eingeleitet. Der Brustkorb des Tieres wurde nicht eröffnet, die Elektrokardiogramme wurden vom rechten Vorder- und linken Hinterbein aufgenommen. In einer asphyktischen Periode wurden die verschiedenen Stadien des Herzblockes beobachtet, und sobald sich der komplette Herzblock einstellte, wurde der eine oder der andere Vagus gereizt und der Erfolg verzeichnet. Wiederum wurde die künstliche Atmung in Gang gesetzt, worauf sich der normale Rhythmus alsbald herstellte. In den letzten Experimenten wurden Vagi und Sympathici in ihrem Verlaufe am Halse voneinander getrennt und der Vagus allein gereizt. Die Erfolge waren dieselben. Kontrollkurven waren auch unmittelbar vor jeder asphyktischen Periode aufgenommen, so dass der Einfluss der Reizung während der normalen Herzaktion und während des kompletten Herzblocks verglichen werden konnte. Die sekundäre Rolle des Induktionsapparates war immer $3\frac{1}{2}$ cm von der primären entfernt. Diese Distanz hat

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1) Lewis and Mathison, Auriculo-ventricular heart-block as a result of asphyxia. Heart vol. 11 p. 47—54. 1910—1911.

uns bei normaler Herzaktion eine bedeutende Verlangsamung oder Stillstand der Vorhöfe gegeben. Der Einfluss der Vagusreizung auf die Kammer in diesem kompletten Herzblocke war im allgemeinen gleich.

Beobachtungen.

Gewöhnlich verursachte die Vagusreizung während des kompletten Herzblockes eine allmähliche Verlangsamung der Kammerschlagfolge. Diese Wirkung zeigen unsere Tabellen, sowie die Figuren 1, 3, 5 und 6. —

Die Verlangsamung tritt nach verschieden langer Zeit nach dem Beginn der Reizung auf; sie kann fast unmittelbar auftreten, aber gewöhnlich ist sie verzögert und beginnt erst 1—1½ Sekunden nach der Reizung. Diese Werte beziehen sich sowohl auf den rechten wie auf den linken Vagus. Die Verlangsamung dauert während der ganzen Reizperiode an und ist gewöhnlich nach Aufhören der Vagusreizung am bedeutendsten, selbst dann, wenn die Reizung 3—4 Sekunden dauerte. Dann folgt eine Beschleunigung, deren Natur wir später noch eingehender besprechen werden.

Etwas, aber nicht viel seltener ist das Vorkommen von langen Kammerpausen, die 3—3,3 Sek. (rechts) oder 2,7, 3,0, 4,1 Sek. (links) andauern. Wenn wir unsere Kurven von diesem Gesichtspunkte aus durchsehen, können wir zwischen der Wirkung des rechten und linken Vagus keinen Unterschied finden (Fig. 8, 11 und 12). Vor dem Vagusstillstand ist die Vorhof- und Kammerschlagzahl verschieden, aber im allgemeinen kommen ca. 200 Vorhofschläge auf 133 Kammerschläge.

Die Wirkung der Vagusreizung auf den Vorhof ist die bekannte. fast immer steht er während der Reizung still und oft auch ziemlich lange nachher (gleich, ob rechts oder links gereizt wurde); manchmal aber und besonders bei Reizung des linken Vagus ist die Befreiung des Vorhofes von dem Einflusse der Vagusreizung früher zu beobachten (Fig. 8), und in ein oder zwei Fällen hatte die Reizung des linken Vagus nur Vorhofsverlangsamung zur Folge (Fig. 9).

Die vor dem Beginne der Asphyxie aufgenommenen Kontroll-kurven zeigen nicht selten eine geringe Retardation der Kammer-schlagfolge als die während der Vagusreizung im asphyktischen kompletten Herzblock aufgenommenen (Fig. 7, 8 und 10, 11). Dies mag auch der Fall sein, wenn in den Kontrollkurven idioventrikuläre

Beobachtungen [1]).

Reizung des Vago-sympathicus	Vor der Reizung		Während der Reizung	Nach der Reizung
Katze 83.				
Platte III, Beobacht. 1 / links 130[2])	Kompl. Herzblock Vorhof	12[2]) 15 12 15 12 15	Keine Vorhofschläge	
	Kammer	24 24 24	24 24 25 26 27	
Platte IV, Beobacht. 3 / rechts 117	Kompl. Herzblock Vorhof	31 27	keine Vorhofschläge	30
	Kammer	27 27	27 27 28	
Katze 84.				
Platte I u. II, Beobacht. 1 / rechts 148	Kompl. Herzblock Vorhof	8 8 8 8 8	keine Vorhofschläge	17
	Kammer	12 13 12	13 13 14 13 13,5 14 14,5 14,5 15 16	
Platte I u. II, Beobacht. 1 / rechts 169	Kompl. Herzblock Vorhof	9 9	keine Vorhofschläge	
	Kammer	13 13	13 13 13,5 14 15 15 16 16 17 17	
Platte III, Beobacht. 1 / links 133	Kompl. Herzblock Vorhof	11 11	keine Vorhofschläge	19 19 19
	Kammer	13 13	13 14 15 16 17 17 18	
Katze 85.				
Platte II, Beobacht. 1 / rechts 187	Kompl. Herzblock Vorhof	14 14	keine Vorhofschläge	16 30
	Kammer	37 37	50 80 49	
Platte II, Beobacht. 2 / rechts 131	Kompl. Herzblock Vorhof	14 14	keine Vorhofschläge	.
	Kammer	37 37	37 43 108	

1) Wir berichten nur über die Beobachtungen, in welchen kompletter Herzblock vor Beginn der Reizung registriert war.

2) All die Zahlen bedeuten $1/30$ Sekunden.

Reizung des Vago-sympathicus	Vor der Reizung	Während der Reizung	Nach der Reizung
Katze 86. Platte I Beobacht. 1 — rechts 134	Kompl. Herzblock Vorhof 10 10 10 10 10 10 13 13 13 13 Kammer	15 13 14 14 14 14 14 15 15 keine Vorhofschläge 15 15	13 13 11 11 15 15 16 16 15 11 11 11 ... 15 16 16
Platte I Beobacht. 2 — rechts 81	K. Herzblock ohne Vorhofschl. Vorhof Kammer 17 17 17 17	18 18 18 20	24 25 26 25 24 21 22 25
Platte III Beobacht. 1 — rechts 132	Kompl. Herzblock Vorhof 9 9 9 9 9 Kammer 14 14 14 14	14 14 15 15 keine Vorhofschläge 16 16 17 18	1:1 Kompl. Herzblock 12 (×7 Perioden) 10 · · 14 · · 19 19 20 17 12 12
Katze 87. Beobacht. 2 — rechts 136	Kompl. Herzblock Vorhof 13 13 13 Kammer 23 20	27 28 85	36 45 83 33
Beobacht. 3 — links 66	Kompl. Herzblock Vorhof 12 12 12 Kammer 29 23	23 24 27	12 2:1 Herzblock 12 12 12 12 12 24 24 24 35 32 33
Katze 88. Platte 1 — rechts 98 (Reizung des Vagus)	Kompl. Herzblock Vorhof 9 9 9 9 9 9 9 Kammer 14 14 14 14 14	14 15 27 34	Kompl. Herzblock 10 10 10 10 30 92
Platte II Beobacht. 1 — links 90	Kompl. Herzblock Vorhof 10 10 10 10 10 10 10 Kammer 14 14 14 14 14	15 36	2:1 Herzblock 1:1 10 10 10 10 10 13 11 10 10 10 10 21 16 31 24 74
Platte II Beobacht. 2 — links 90	Kompl. Herzblock Vorhof 9 9 9 9 9 Kammer 14 14 14	16 28	2:1 Herzblock 11 11 11 11 11 11 12 11 11 11 11 22 22 22 22 15 12 12 11 17 17 15 12 81

	Reizung des Vagus	Vor der Reizung	Während der Reizung	Nach der Reizung
Katze 88.				
Platte III Beobacht. 1	links 27	Kompl. Herzblock Vorhof 9 9 9 9 9 Kammer 14 14 14 15	16 16 17 15	13 11 11 11 11 11 11 10 10 35 24 21 13 19 11
Platte III Beobacht. 2	rechts 57	Kompl. Herzblock Vorhof 10 10 10 10 10 10 Kammer 15 15 15 15	16 34	13 13 13 13 124 13 12
Platte IV	rechts 52	Kompl. Herzblock Vorhof 10 10 10 10 10 Kammer 15 15 15	16 32	in kompl. Herzblock 10 10 10 10 10 10 10 12 22 23 13 23 100
Platte IV Kontrolle³)	rechts 82	Vorhof 8 8 8 8 8 8 Kammer 8 8 8 8 8	8 17 20 44 13¹) 14¹) 14 15¹) 17¹) 12	16 12 10 9 9 9 8 ·· ·· 16 12 10 9 9 9 8 ·· ··
Platte VI	links 87	Kompl. Herzblock Vorhof 10 10 10 10 Kammer 16 16	16 18 43 20 12	2:1 Herzblock 15 14 13 12 12 12 12 25 23
Platte VI Kontrolle³)	links 68	Vorhof 11 11 11 11 Kammer 11 11 11	17 41 18 26 20 20	1:1 Herzblock 15 15 ·· ·· 15 15 ·· ·· 1 : 1 12 ·· ·· 12 ·· ··
Katze 89.				
Platte I	rechts 76	Kompl. Herzblock Vorhof 10 10 10 10 10 10 Kammer 16 16 16 16	16 16 17 18 keine Vorhofschläge 22	22 22 22 22 22 8 8 ·· ·· 8 8 ·· ··
Platte I Kontrolle³)	rechts 67	Vorhof 7 7 7 7 7 7 Kammer 7 7 7 7 7	12 12 12 keine Vorhofschläge 12²)	13 13 14 13²)

1) Linksseitige Kammerschläge.
2) Alle rechtsseitige Kammerschläge.
3) Vor der asphyktischen Periode.

Reizung des Vagus	Vor der Reizung	Während der Reizung	Nach der Reizung
Katze 89. Platte II	Kompl. Herzblock Vorhof 11 11 11 11 11 11 11 Kammer 17 17 17 17 17 17	keine Vorhofschläge 18 23 17	keine Vorhofschläge 23 23 23 23 23 23 23 23 23 25 25
Platte II Kontrolle[5]	Vorhof 8 8 8 8 8 8 8 8 Kammer 8 8 8 8 8 8 8	keine Vorhofschläge 12 12 13 14 14 15 15[1] 17	keine Vorhofschläge 16 17 8 8 8 8 9[1] 8 8
Platte III	Kompl. Herzblock Vorhof 11 11 11 11 11 Kammer 18 18 10 22	17 20 55 31 19 32 34	20 18 14 14 13 13 13 13 13 13 38 46 33 26
Platte III Kontrolle[5]	Vorhof 8 8 8 8 8 8 8 8 Kammer 8 8 8 8 8 8 8 8	10 12 14 16 17 18 19 9 47[2] 81	19 14 10 10 10 10 10 10 25 21
Platte IV	Kompl. Herzblock ohne Vorhofschl. Vorhof Kammer 22 22	22 21 29 30 32	35 39 40 38 36
Platte IV Kontrolle[5]	Vorhof 7 7 7 7 7 7 7 Kammer 7 7 7 7 7 7 7	9 11 12 29 40 20 13 26[3] 33[3] 52	17 13 10 10 10 9 9 17 22 13 10
Platte VI	Kompl. Herzblock Vorhof 17 17 17 Kammer 20 16	keine Vorhofschläge 29 35 38 44	18 14 12 49 52 48 18 24 55
Platte VI Kontrolle[5]	Vorhof 9 9 9 9 9 9 Kammer 9 9 9 9 9 9	11 12 17 22 24 24 26[4] 89	11 11 11 11 11 10 10 11 11 11 11 10 10

1) Alle rechtsseitige Kammerschläge.
2) Eine linksseitige Kammerkontraktion.
3) Linksseitige Kammerschläge.
4) Eine linksseitige Kammerkontraktion.
5) Vor der asphyktischen Periode.

Reizung des Vagus		Vor der Reizung	Während der Reizung	Nach der Reizung
Katze 90. Platte I	rechts 108	Kompl. Herzblock	keine Vorhofschläge	
		Vorhof 9 9 9 9 9 9 22 22	22 22 23 25 26	21 16 13 13 11 11 10 10 10 10 10
		Kammer 22 22		28 28 28 27 26 24 24
Platte I Kontrolle[2]	rechts 80	Vorhof 10 10 10 10 10 10	keine Vorhofschläge 12	10 18 12 10 11 12 13 13 12 ...
		Kammer 10 10 10 10 10 10	20 20 22 22 24[1]	11[1] 17 12 10 11 12 13 13 12 ...
Platte II	links 136	Kompl. Herzblock	keine Vorhofschläge	
		Vorhof 11 11 11 11 11 11		11 11 11 11 11 11 11
		Kammer 26 26 26	26 26 28 32 135	36
Platte II Kontrolle[2]	links 99	Vorhof 12 12	keine Vorhofschläge 12[1] 24[1] 28[1] 57	31 13 15 15 15 ...
		Kammer 12 12	12	16 13 15 15 15 ...
Platte III	links 175	Kompl. Herzblock ohne Vorhofschl.		Eine volle normale Kontraktion 105 17
		Vorhof 27 27	28 31 123	
		Kammer 27 27	12 12	
Platte III Kontrolle[2]	links 90	Vorhof 8 8 8 8 8 8 8 8	8 20 25 26 27	27 16 13 10 10 ...
		Kammer 8 8 8 8 8 8 8 8	8 13 12 13 13 13 13 14	14 14 11 10 10 ...

1) Rechtsseitige Kammerschläge.
2) Vor der asphyktischen Periode.

Kontraktionen erscheinen (Fig. 7). Die Kontrollkurven zeigen während
der Vagusreizung fast immer Kammerelektrokardiogramme. die dem
Typus der von der rechten
oder linken Seite aus-
gehenden Kontraktionen
gleichen, indessen sehen
wir solche anomale Schläge
niemals in den Kurven des
kompletten Herzblocks.
In dieser Beziehung ist
der Gegensatz ziemlich ins
Auge fallend (Fig. 4, 5 und
10, 11).

Wo in einer asphyk-
tischen Periode der kom-
plette Herzblock sich ein-
mal einstellt, bleibt er
so lange bestehen, bis
alle Zeichen der Vorhof-
kontraktionen plötzlich
verschwinden; wir be-
tonen, dass ein Herz, das
einmal im Zustande des
kompletten Herzblockes
war, während einer Be-
obachtung in Asphyxie
wenig oder keine Ten-
denz zur Aufnahme eines
Mechanismus im Sinne
einer geringer gestörten
Reizleitung zeigt. Ist aber
der Vagus gereizt, so sehen
wir ein anderes Verhalten.
Nach dem Kammerstill-
stande hat sich der kom-
plette Herzblock zu einem
2 : 1 Block reduziert oder

Fig. 1. Katze 86. Platte 1. Beobachtung 1. Elektrokardiogramm 2 Minuten nach Beginn der Asphyxie. Die ersten Perioden zeigen den kompletten Herzblock. Vorhof und Kammer schlagen regelmässig, aber mehrere Vorhofserhebungen sitzen auf den Kammerkurven. Mit Beginn der Reizung des rechten Vagosympathicus schwindet die Vorhofserhebung (siehe Signal). Der Kammerrhythmus wird etwa nach 1 Sekunde langsamer; im Anfang ist die Verlangsamung sehr gering, doch wird dieselbe nach Beendigung der Reizung bedeutender. Nun folgt wieder kompletter Herzblock, wonach sich dann plötzlich der normale Rhythmus einstellt. Oben ist die Zeitschreibung ¹⁄₆-Sekunden, und unter dem Reizsignal bedeutet sie ⅒-Sekunden. 2 mm 10 ⁻¹ Volt. Dieselben Daten beziehen sich auch auf die weiteren Figuren.

der normale Rhythmus Platz gegriffen. Das ist deutlich in Fig. 1. 3.
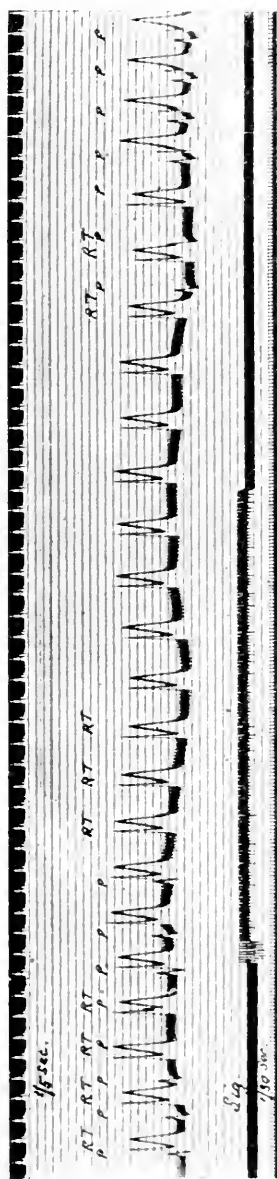8 und 9 zu sehen, die Reizleitung stellt sich aber nicht wieder her

(Fig. 6), und wenn dies der Fall ist, so ist es nur kurz dauernd, und rasch tritt wieder kompletter Herzblock auf (Fig. 3). —
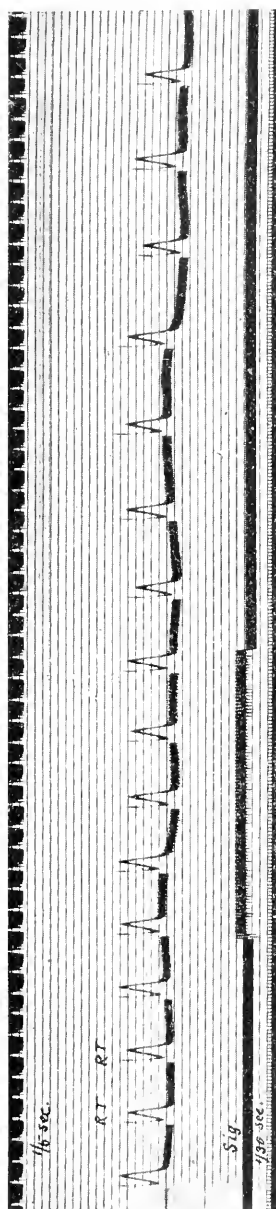
Fig. 2. Katze 86. Platte II. Beobachtung 2. Ein Elektrokardiogramm von demselben Tier: 2½ Minuten nach Beginn einer Asphyxie-Periode. Vorhof und Kammer schlagen unabhängig voneinander; die Vorhofkontraktionen sind bereits verschwunden. Reizung des rechten Vagosympathicus verursacht eine ganz ähnliche Verlangsamung, wie wir dies in Fig. 1 gesehen haben.
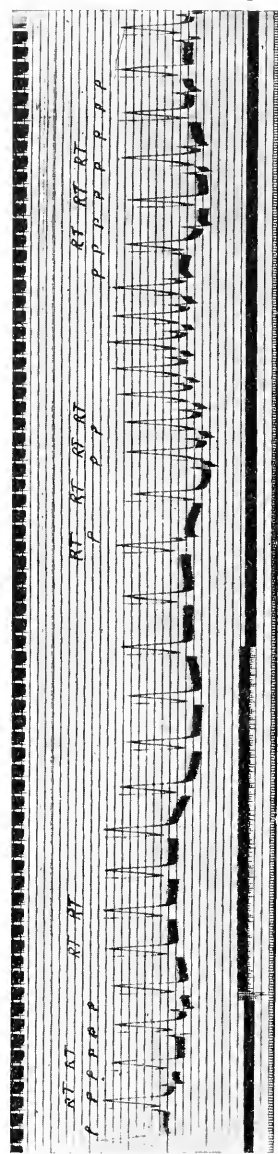
Fig. 3. Katze 86. Platte III. Beobachtung 1. Elektrokardiogramm von demselben Tier; 2 Minuten nach Beginn der Asphyxie. Vor dem Beginne der Reizung sehen wir den kompletten Herzblock; während der Reizung des rechten Vagus sistieren die Vorhofsschläge, die Kammern schlagen in einer immer langsamer werdenden Folge weiter. Zu beachten ist die temporäre Wiederherstellung des normalen Rhythmus (als Folge der Vagusreizung), nachher wieder Dissoziation.

Die „Spinal-Katze" zeigt in der Asphyxie nach dem Stadium des kompletten Herzblockes ein weiteres, in welchem, während die

regulären Kammerschläge fortdauern, die Vorhofschläge verschwinden. Der Kammerrhythmus hat sonst dieselbe Eigenschaft wie im kom-
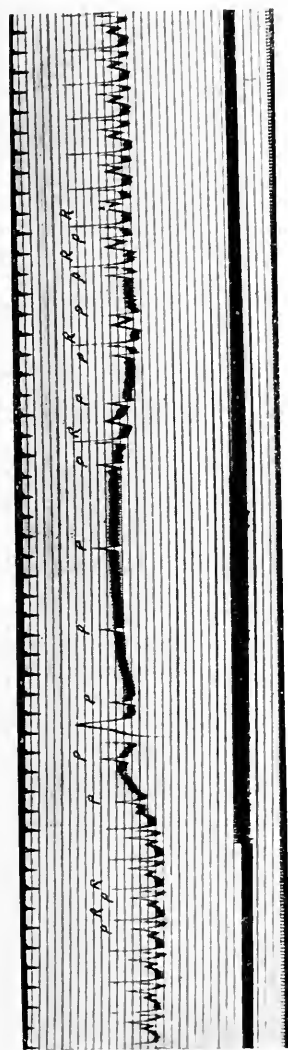
Fig. 4.
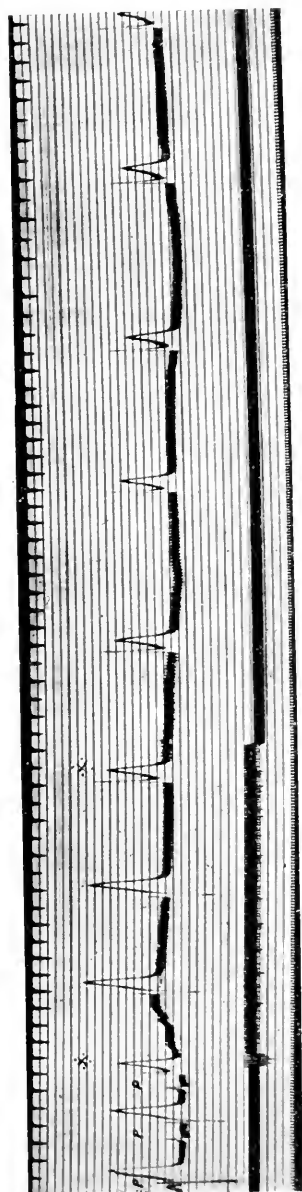
Fig. 5.

Fig. 4 und 5. Katze 89. Platte VI. Beobachtung 1 und 2. Reizung des linken Vagus unmittelbar vor und 3 Minuten nach Beginn einer Asphyxie-Periode. Fig. 4. Mit der Reizung des Vagus wird der normale Rhythmus gestört. Der Vorhof zeigt eine fortschreitende Verlangsamung, und unterdessen ist nur eine einzige linksseitige anomale Kammerkontraktion zu sehen. Am Ende der Kurve sehen wir den Übergang eines 2:1 Herzblockes zum normalen Rhythmus. Fig. 5. Im Momente der Reizung ist kompletter Herzblock vorhanden. Der Vorhof hört auf zu schlagen, und es ist auch die Verlangsamung der Kammeraktion zu sehen. Zu beachten ist der veränderte Typus der Kammerkontraktionen; dies rührt nicht von der Vagusreizung her, sondern von der Asphyxie. Die Veränderungen infolge der Asphyxie sind nicht selten, und wir bekommen dieselben auch ohne eine Vagusreizung zu sehen.

pletten Herzblocke. Aus diesem Stadium der Asphyxie ist die Wiederherstellung selten. Die Vagusreizung hat ganz denselben Effekt auf

den Kammerrhythmus (obwohl die Vorhofkontraktionen fehlen), wie während des Stadiums der Dissoziation, Fig. 2 und 13).

Fig. 6. Katze 90. Platte I. Beobachtung 2. Reizung des rechten Vagu 3 Minuten 5 Sekunden nach Beginn der Asphyxie. Vorhof und Ventrikel schlagen dissoziiert; mit der Reizung verschwinden die Vorhofkontraktionen und wird der Kammerrhythmus verlangsamt. Nach der Reizung stellt sich der komplette Herzblock wieder ein, und es folgt eine graduelle Beschleunigung der Herzaktion.

Besprechung.

Wir haben gesehen, dass die Vagusreizung (rechts oder links) den Rhythmus der Kontraktionen der isolierten Herzkammer ausgesprochen ändert. Bei normalem Rhythmus erfolgt während der Zeit der Vagusreizung Kammerverlangsamung oder Kammerstillstand als die natürliche Folge von (1) Vorhofstillstand oder (2) von einem Herzblock. Aber die Wirkungen der Vagusreizung im kompletten Herzblocke sind in einer anderen Weise zu deuten, wie wir dies sehen werden. Diese sind die Folgen von einer direkten Vaguswirkung (rechts oder links) auf den „Pacemaker" der Kammer; die natürliche Reizerzeugung in diesem Zentrum steht unter Vaguskontrolle.

Die Ergebnisse unserer Experimente beweisen diese Tatsache für die Katze und bestätigen den Befund Hering's bei einem Kaninchen und Rihl's und Fredericq's beim Hund. Die Frage des Vagusverlaufes können wir nicht diskutieren, unsere Beobachtungen werfen nur geringes Licht auf sie. Wahrscheinlich sind im asphyktischen kompletten Herzblock alle Vagusnervenwege offen; gewiss sind es jene, die zum

normalen Zentrum der Reizerzeugung im Vorhofe gehen: wir erhielten ja immer Vorhofverlangsamung oder Stillstand. Frühere

Fig. 7.

Fig. 8.
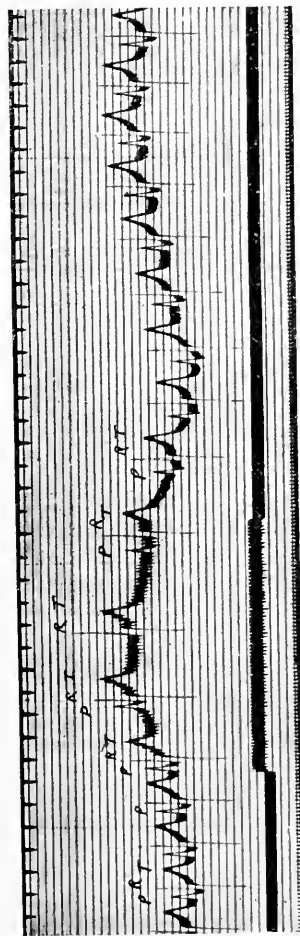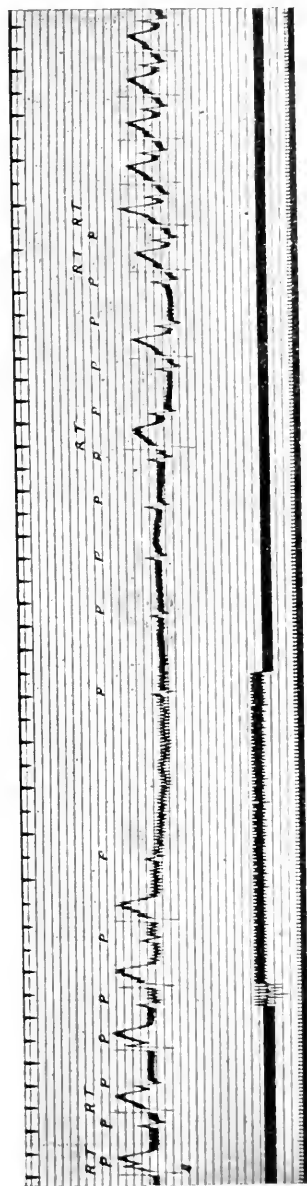
Fig. 7 und 8. Katze 88. Platte VI. Beobachtung 1 und 2. Reizung des linken Vagus direkt vor und 2 Minuten 35 Sekunden nach Beginn derselben asphyktischen Periode. Fig. 7 zeigt den normalen Rhythmus. Die Vorhof- und Kammerausschläge werden verlangsamt. Es ist hier eine automatische Kammerkontraktion zu sehen (wahrscheinlich verdankt sie ihr Entstehen der Vagusreizung). Fig. 8 zeigt kompletten Herzblock vor, Verlangsamung der Vorhofe und dann normale Schlagfolge stand der Kammer während der Reizung. Nach der Reizung sehen wir einen 2:1 Herzblock und dann normale Schlagfolge

Untersuchungen scheinen alle darüber im Einklange zu stehen. dass, wenn das Bündel vollständig getrennt ist, die Vagi wenig

oder keinen Einfluss auf den automatischen Kammerrhythmus
haben [die einzige Ausnahme bildet Rihl's zweite Beobachtung[1])].
Jedoch, dass auch so irgendein Effekt auftritt, zeigen auch die Kurven
von Erlanger. Es ist also möglich, dass manche Vagusfaser viel-
leicht auf einem anderen Wege als die des Bündels zur Kammer
gelangen. Gleichzeitig aber befestigen uns eben unsere Beobachtungen
in der Ansicht, dass die meisten der Vagusfasern in dem Bündel
verlaufen. In Hering's Versuchen an Kaninchen war das Bündel nur
abgeschnürt und wieder von der Schnur befreit, und in Fredericq's
Versuchen an Hunden heisst es, dass das Bündel nur bis zu einem
gewissen Grade komprimiert war. In all diesen Experimenten hatte
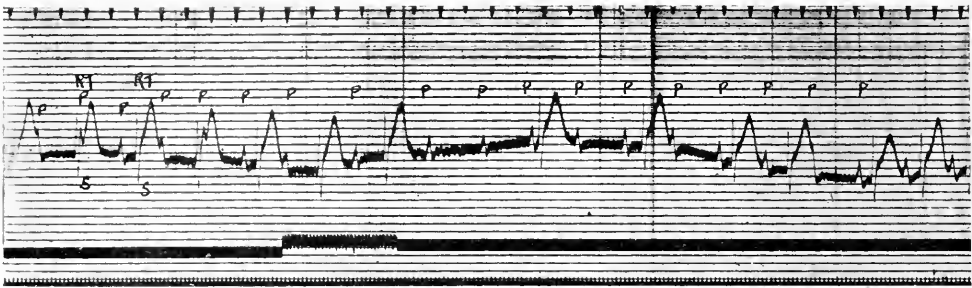
Fig. 9. Katze 88. Platte III. Beobachtung 1. Reizung des linken Vagus
2 Minuten und 40 Sekunden nach Beginn der Asphyxie. Mässige Verlang-
samung der Vorhöfe und starke Verlangsamung der Kammeraktion. Die Wieder-
herstellung geschieht in partiellem Herzblocke.

die Vagusreizung eine tiefgreifende Wirkung. In unseren eigenen
Experimenten, wo die Nervenfasern des Bündels wahrscheinlich un-
verletzt blieben, war der Effekt ebenfalls tiefgreifend.

Wir beabsichtigten aber Beweise für die Tatsache zu bringen,
dass die Vagi den Kammer-„Pacemaker" in der Katze beeinflussen,
und nicht die Wege zu isolieren, durch welche die nervösen Impulse
zur Kammer gelangen.

Es bleibt noch eine Möglichkeit der Erklärung übrig, die wir
zu besprechen haben. Erlanger meint, dass, wenn auch eine Ver-
langsamung im Kammerrhythmus sich einstellt, dies sekundär durch
den Vorhofstillstand verursacht wird, selbst dann, wenn eine kom-
plette Dissoziation zwischen den beiden Herzteilen besteht. Die Art
und Weise, wie wir uns das vorstellen sollen, ist bei Erlanger

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1) Es ist möglich, dass das Bündel hier nicht vollständig destruiert war.

nicht gesagt.   Diese Auffassung könnte man indessen schwerlich
irgendwie unterstützen.   Es scheint uns, dass die vorliegenden
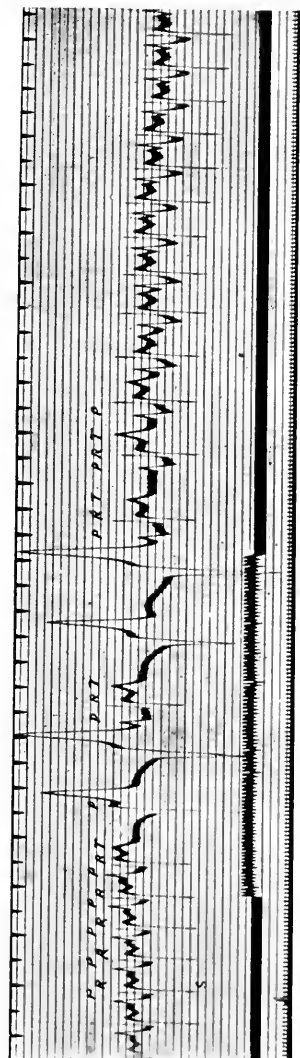
Fig. 10.
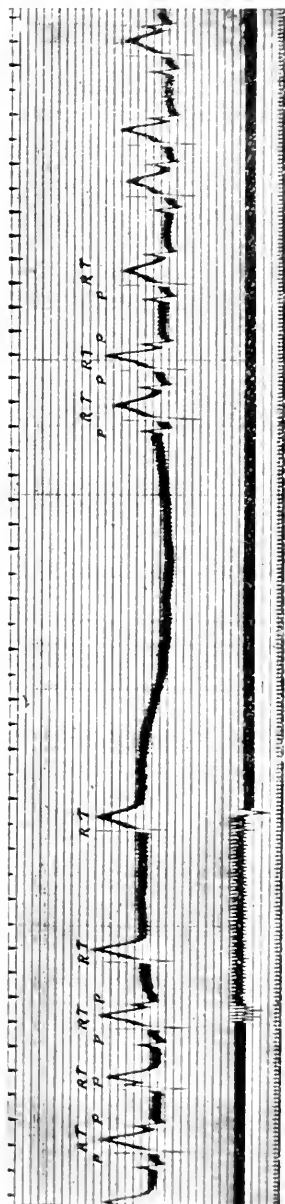
Fig. 11.

Fig. 10 und 11. Katze 88. Platte IV. Beobachtung 1 und 2. Reizung des rechten Vagus unmittelbar vor und 2 Minuten 35 Sekunden nach Beginn der Asphyxie. Fig. 10 zeigt die Störung des normalen Rhythmus. Man sieht eine Verlangsamung, und es treten linksseitige Kammerkontraktionen auf. Fig. 11 zeigt kompletten Herzblock. Reizung verursacht Stillstand des Vorhofes und der Kammer. Nachher sehen wir partiellen Herzblock.

Experimente diesen Faktor endgültig ausschliessen.   Die Kammer-
verlangsamung ist ja nicht proportional der Vorhofverlangsamung, die

2

letztere kann ganz gering sein, wo die erstere vielleicht am be-
deutendsten ist (Fig. 8 und 9). Wiederum dort, wo der Kammer-
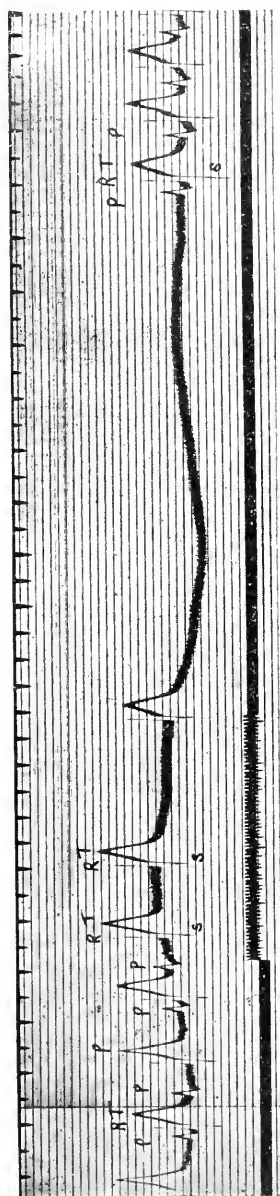
Fig. 12. Katze 88. Platte III. Beobachtung 2. Reizung des rechten Vagus 2 Minuten 5 Sekunden nach Beginn der Asphyxie. Kompletter Herzblock vor der Reizung; die Reizung verursacht Stillstand des Vorhofes und der Kammer. Nach der Reizung ist normale Schlagfolge zu sehen, doch entwickelt sich der Herzblock wieder.
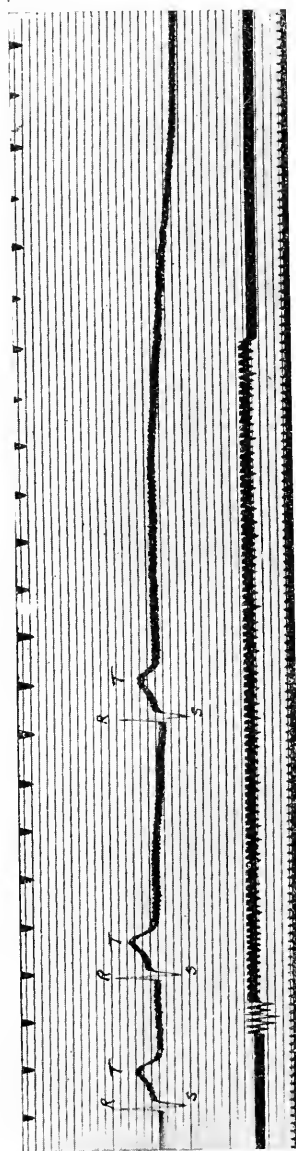
Fig. 13. Katze 88. Platte V. Beobachtung 2. Reizung des rechten Vagus 2 Minuten 15 Sekunden nach Beginn der Asphyxie. Die Kammer schlug regelmässig im Momente der Reizung, die Vohofschläge fehlen. Die Reizung verursacht Kammerstillstand.

hrythmus in Asphyxie nach Vorhofstillstand weiter fortdauert, sehen
wir im Momente des plötzlichen Verschwindens der Vorhofkontraktionen

keinen Kammerstillstand auftreten, und die Vagusreizung beeinflusst diesen unkomplizierten Kammerrhythmus ganz in derselben Weise wie den Kammerrhythmus dort, wo die Vorhöfe noch aktiv waren. Folgerichtig ist der Vorhofstillstand während der Vagusreizung ohne Einfluss auf die Verlangsamung oder auf den Stillstand des dissoziierten Kammerrhythmus.

Die Beobachtung, dass der Vagus den idio-ventrikulären Rhythmus beeinflusst, ist in Übereinstimmung mit der Erfahrung, dass die spontanen Kammerrhythmen, die durch Vergiftung oder Anämie entstanden sind, auch durch den Vagus beeinflusst werden.

Noch eine Nachwirkung der Vagusreizung wäre hier zu erwähnen. Wir haben gesagt, dass der Grad des Herzblocks ein niedrigerer ist nach der Vagusreizung. Aus früheren Beobachtungen von Lewis und Oppenheimer[2]) wissen wir, dass inhibitorische Impulse den Grad eines asphyktischen Blockes erhöhen, die Nachwirkung ist aber eine entgegengesetzte. Solche im entgegengesetzten Sinne nach der Vagusreizung auftretende Effekte sind bei Gaskell[3]) beschrieben. Wir folgen ihm, wenn wir in der Aufhebung des asphyktischen Herzblockes einen anabolischen Prozess erblicken, welcher als eine sekundäre Erscheinung auf den prädominierenden katabolischen Prozess am Beginne der Reizung folgt.

Wir haben schon erwähnt, dass bei der Vagusreizung während des kompletten Herzblockes der Asphyxie nie die anomalen rechts- oder linksseitigen Kammerkontraktionen auftreten, welche in den Kontrollkurven so auffallend sind. Die Bedeutung dieser Erscheinung ist uns nicht klar, gewissermaassen erklärt sie aber die Beobachtung, dass Kammerverlangsamung während des kompletten Herzblockes unter dem Einflusse der Vagusreizung oft grösser ist als während der normalen Herzaktion. Die besonderen automatischen Schläge scheinen für die relative rasche Kammeraktion, wenn sonst kein Herzblock besteht, verantwortlich zu sein. Wenn anomale Kontraktionen fehlen, so sind manchmal automatische Kammerschläge

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1) Erlanger and Blackman, Further studies in the physiology of heartblock in mammals. Chronic auriculo-ventricular heart-block in the dog. Heart vol. 1 p. 177—220. 1909—1910.

2) Lewis and Oppenheimer, The influence of certain factors upon asphyxial heart-block. Journ. of med. vol. 4 p. 145—152. 1910—1911.

3) Gaskell, On the innervation of the heart, with especial reference to the heart of the tortoise. Journ. of Physiol. vol. 4 p. 43—127. 1883.

zu sehen, welche normale elektrische Kurven geben. Dieser Kontrast zwischen den Kurven des Experiments und den Kontrollkurven lässt vermuten, dass diese anomalen und auch diese automatischen Schläge, da sie während einfacher Vagusreizung auftreten, eben infolge Vagusreizung entstanden sind.

Zum Schluss ist es mir ein tiefgefühltes Bedürfnis, Herrn Dr. Th. Lewis für die mir erteilte gütige Erlaubnis zur Bearbeitung des Themas in seinem Institut sowie für die durch ihn ausgeführten Vivisektionen meinen wärmsten Dank auszusprechen.

A DESCRIPTION OF A CASE OF COMPLETE HEART-BLOCK. INCLUDING THE POST-MORTEM EXAMINATION.

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AND

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A MINISTER, aged 77, who was a patient of Dr. C. E. McDade, was brought to University College Hospital Medical School in March, 1911, for electro-cardiographic examination, through the kindness of Dr. H. Batty Shaw.

He had been under Dr. McDade's care for a number of years, and his condition was reported in the *Lancet, 1906, ii, page 653.*

The patient was an extremely hard working man who had had excellent health until 1904, when he was 70 years of age.† In July of that year and in February, 1905, he had attacks of vertigo and flatulence. In June, 1905, the pulse rate was noticed to be 40 ; the beats were strong and regular. He complained of easy exhaustion, especially after exertion. There was then no vertigo, and breathing was free and the urine normal. The heart sounds were clear. On June the 23rd, the pulse beat regularly at 78. From July the 7th to 14th, the pulse beat regularly at 40 and he was performing his usual arduous work without fatigue. On August the 13th, the pulse was regular at 63, and on November the 13th, regular at 38. On December the 15th he seemed to be failing in strength. The pulse was 32 and sometimes irregular. He took to bed on the 19th and the pulse became regular again, varying in rate from 28 to 32. At this time rapid oscillations of the jugular veins were seen. On January the 25th, 1906, a trace of albumen was found in the urine ; the pulse remained slow. On February the 5th the rate was 63, the beats being regular. For the next four weeks it varied between 48 and 80. By March the 15th, 1906, the pulse rate was normal and active work was resumed in May.

The patient's condition remained satisfactory till October, 1907, when the pulse again fell to 40 and continued at or about this rate until May, 1908. Most of this period was spent in bed or indoors. Albuminurea was present at this time. There had been no further attacks of vertigo.

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* Working under tho tenure of a Beit Memorial Fellowship.
† For these notes we are indebted to Dr. McDade and to his *Lancet* report.

From May to November, 1908, the pulse was normal and the albuminurea vanished, work being resumed. In November, 1908, the pulse rate fell to 37 and continued at or about the rate of 34 until death occurred in April, 1911. The albuminurea also reappeared and was maintained ; moreover the feet and legs became swollen and this condition persisted. At this time the systolic blood pressure was measured at 220 mm. Hg..

On October the 22nd, 1910, a cough developed and strained him a good deal ; and a few days later he had a fit of unconsciousness accompanied by lividity.

From January to March, 1911, feebleness increased. Oedema of the ankles and albuminurea were continuously present.

On March the 24th he came to University College Hospital Medical School. The curves, which are reproduced (Fig. 1) demonstrated complete heart-block ; the auricular rate was 88 and the ventricular 34. The shape of the ventricular complexes in the three leads was such as is said to indicate hypertrophy of the left ventricle. At this time there was a good deal of breathlessness. With the exception of a systolic apical murmur, the sounds were normal.

In the morning of April the 5th, 1911, he complained of " stupid feelings " in the head ; in the afternoon he became gradually comatose and died.

The post-mortem, which was performed by Dr. McDade, was limited to the heart and aorta. The latter were very atheromatous. The heart was fixed in Müller-Formol, as described in previous communications.

Macroscopic anatomy of the heart.

The ventricle measures 13 cm. anteriorly from the *A-V* groove to the apex and 11·5 cm. posteriorly. Its weight is 732 grammes.

On the surface of the heart, more especially over the right ventricle, there is a layer of more than the normal amount of fatty tissue. The pericardium in numerous places is thicker and whiter than normal. The right auricle is dilated a little and the endocardium is opaque. The tænia terminalis is not hypertrophied. The tricuspid valve admits four fingers easily ; its edges are thickened. The cavity of the right ventricle is not enlarged. The muscle breaks easily under the finger. There are no ante-mortem dots in any of the chambers. Its wall measures 6 mm. at the base, and 6 mm. at the conus arteriosus. The corpora Arantii of the pulmonary valve are slightly thickened. The left auricle is considerably dilated ; its endocardium is white, thick and smooth. The mitral valve admits three fingers in line. The edges are thick like those of the tricuspid valve. The aortic flap of the mitral valve shows advanced atheroma. The cavity of the left ventricle is slightly dilated, the dilatation being most prominent below the aorta in the outflow tract. The wall at the venous base measures 15 mm., at the level of the papillary muscles it measures 16 mm., and at the apex 10 mm. The trabeculæ are flattened. The endocardium over them is

Fig. 1.
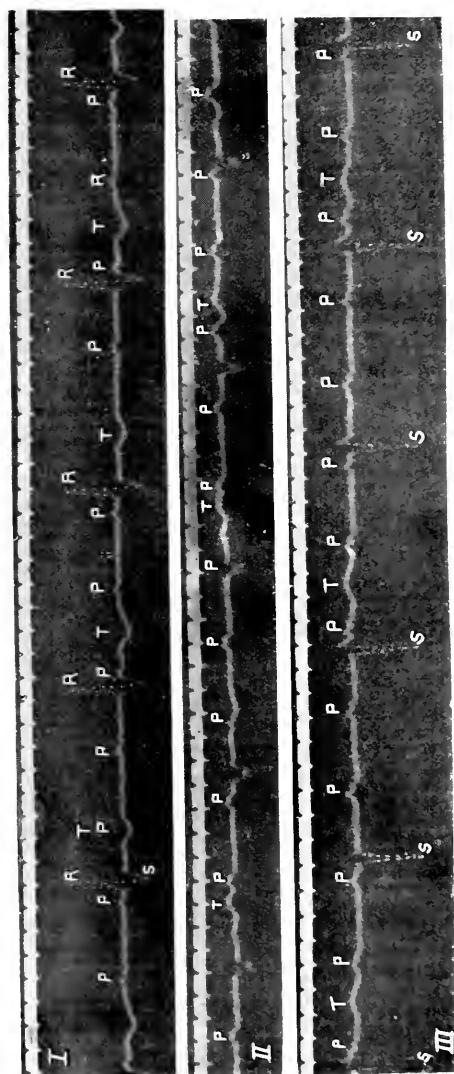
smooth and thin, but that covering the membranous septum and the adjoining areas is very thick and firm. The corpora Arantii of the aortic cusps are thick and at their attached margins their density is cartilaginous : they were slightly incompetent in the fresh state. The anterior sinus of Valsalva, the line of attachment of the aortic cusp, is calcareous. The other sinuses of Valsalva present an advanced athero-sclerosis. Advanced athero-sclerosis is also found in the coronary arteries. The descending branch of the left coronary artery shows a calcareous plaque near its origin, and also farther along in the course of the vessel. Similar changes are found in the right coronary vessel. The lesions do not constrict the lumen of these vessels. There is no lesion at or near the septum membranaceum to indicate that the *A-V* system has been compromised. The foramen ovale is closed. Tissues were excised for microscopic examination :—(1) Two pieces of the wall of the left ventricle, (2) a block of tissue at the junction of the superior vena cava and the right auricular appendix, containing the sino-auricular node, (3) a block of tissue from the interventricular septum, containing the *A-V* node, main stem and the upper portions of the right and left branches of the *A-V* bundle.

Microscopic examination.

Pieces of tissue from the left ventricle show many connective tissue scars, in which the muscle fibres are either atrophic or destroyed.

Sino-auricular node.—This node is found in 2,140 sections. Of these 1,000 were cut 8 micra and 1,140 were 9 micra thick. The total length of this node is therefore 18,260 micra or 18·26 mm.. It lies 2 mm. from the pericardium. At the point where it is first seen, the superior vena cava has already joined the right auricular appendix, so that it begins below the level of the angle of this junction. Actually the superior vena cava still shows its complete lumen and it has not yet widened out into the cavity of the right auricle. The node therefore does not lie in the wall of the superior vena cava. In the upper portions it consists of little more than loose-meshed connective tissue which contains about a half-dozen thin and somewhat elongated muscle fibres. It is completely surrounded by fatty tissue. Large nerve trunks and a small vessel lie in its immediate neighbourhood. At a slightly lower level the node lies 1·5 mm. from the pericardium, measures 2·5 mm. from side to side, and extends for 1·5 mm. into the substance of the auricular wall. Its shape is roughly triangular. The pericardium over the node is thick. The size of the artery to the node has increased : the adventitia is hypertrophied. The various structures which form the node differ from the description usually given, because there is very little interlacement. Its muscle fibres sometimes contain vacuoles. At a still lower level, the vessels to the node, both artery and vein, are prominent and occupy the greater portion of its structure. Its position, size and shape remain unchanged. At its upper extremity it is almost completely surrounded by fatty tissue so that it has an island-like appearance. Farther down the

shape becomes more definitely triangular ; it lies 2·5 mm. from the peri-
cardium and measures 2·5 mm. from side to side, and is 3 mm. deep.   The
apex of this roughly triangular structure communicates freely with the
auricular muscle.   At a still lower level, the node is flatter and longer, the
long diameter being parallel to the pericardium ; it is 1 mm. deep and lies
only 1·5 mm. from the pericardium.   The tail, the lowest level of the
node, is about 2 mm. from the pericardium and measures 1·5 mm. by 1·5
mm. ; its shape is triangular as in the upper levels.

To sum up, the node is almost 2 cm. in length in the fixed state.   It
lies close under the pericardium through its whole extent.   It is first seen
at the angle where the superior vena cava joins the right auricular appendix,
but it does not extend so high as to lie in the wall of the superior vena cava.
Its shape above is first roughly triangular, but at lower levels it is flattened
and elongated, while the tail is again triangular. The node is peculiar in that
the amount of contained muscle tissue is small relative to the size of the
entire structure and that the fibres interlace very little.   There is a good
deal of connective tissue, but the amount is within the limits of normal
variation.   It is also peculiar because it is isolated in so large a part of its
length by fatty tissue.   A feature of the artery to the node which is commented
on by Oppenheimer is shown in this case.   It consists of the presence of small
bundles of muscle, arranged in longitudinal fashion, outside the inner circular
layer of the media.   The arrangement is similar to that seen in the central
veins of the suprarenal gland.

The auricular and ventricular septa.—The cross section of the inter-
auricular septum, the plane of the section being at right angles to the long
axis of the heart, shows an unusual preponderance of fatty and connective
tissues, over the muscle, which usually forms its substance.   This change
in relation is more apparent in the dorsal portions.   In the interventricular
septum numerous scars formed of dense connective tissue, some of which
have undergone hyaline degeneration, are seen at all levels.   In these
scars, the muscle tissue is either atrophic or destroyed.   The muscle fibres
which form the interauricular septum vary a great deal in their diameter.
Their nuclei are different in size and the perinuclear space is wide and free
from muscle fibrils, so that the general appearance of the fibres suggests
that of Purkinje cells.   These fibres are neither grouped nor arranged in a
specific order, so that it is impossible to attribute a separate function to
them, as has been done.   They represent a variety of muscle atrophy.   The
vessels of the septum, more especially the posterior coronary artery, show
an advanced grade of athero-sclerosis.   Advanced sclerosis is also seen at the
root of the aorta, more especially in the sinus of Valsalva of the left posterior
flap.   In the corpus Arantii of one of the aortic cusps, cholestrin crystal
spaces are seen.   There is no evidence of recent inflammation.

The auriculo-ventricular node lies, as usual, to the right of the central
fibrous body, it is very small, and is compressed laterally.   It communicates

with the auricular muscle (the auriculo-nodal junction) by means of a well developed strand of muscle to the left, but by a much attenuated strand to the right. In the upper levels the relative size of these two strands is the reverse of the usual condition, but lower down it is normal. Between the two strands a mass of fatty tissue is found, continuous with the fatty tissue described in the interauricular septum. The auriculo-nodal junction and the auriculo-ventricular node itself are smaller than normal. The node is recognised mainly from its position. The fibres do not interlace in the usual fashion, they are coarser and do not show the normal number of nuclei. The artery commonly found in relation to the node is wanting. Near the node, however, a vessel is found, the structure of which, in contrast to that of the other arteries at this level, is normal. Thus, the continuity of the muscle structure from the auricle to the main stem of the *A-V* bundle, is maintained by a node which in appearance differs little from the auricular muscle. At the transition from the node to the *main stem* of the auriculo-ventricular bundle, there are masses of dense connective tissue. In addition to these there is much loose-meshed connective tissue separating the individual muscle fibres. A number of blood sinuses are also found. They consist of a single layer of endothelial cells surrounded by walls of dense connective tissue, free from muscle. They occupy a considerable portion of the bundle, while the number of muscle fibres is very much reduced. After a short course in the membranous septum, the main stem lies under the endocardium of the left ventricle. A portion of the fibres now passes dorsally and lies between the endocardium of the left ventricle and the lowermost portion of the central fibrous body. This branch, thin and small at its origin, spreads out later under the endocardium and comprises the left branch. At a lower level the mass of tissue forming it becomes greater. Compared with the left branch, the right branch is large, although the number of muscle fibres contained in it is relatively small. The pathological change, consisting of the old connective tissue and blood sinuses described in the main stem, is continued in the right branch to the lowest level examined. Here few muscle fibres are seen in it and the entire structure is very small. At this level the left branch is well developed and presents no abnormality. The smooth muscle fibres, which are described by Nagayo and which are found in the endocardium of the left ventricle and between it and the *A-V* system which lies in the outflow tract, is well developed. The fibres of the left branch show vacuoles. The difference in colour between the muscle of the conducting system and the myocardium is well seen in this case.

To sum up, in the conducting system of this heart the auricular nodal junction is smaller than usual. The auriculo-ventricular node is flattened and small and it is not characteristic either in the arrangement of its muscle or in the nature of its fibres. The main stem and the right branch show conspicuous pathological lesions. The lower portions of the right branch show that this structure is partially atrophic. The left branch is small above and larger below ; it presents no serious lesion. A complete transverse

lesion is therefore absent.   The area of the muscle in the bundle, seen in the
cross section, is seriously reduced by connective tissue formation and by
the presence of the sinuses described.   There is no evidence of an acute or
subacute process.   The lesions are manifestly chronic.

Summary.

A case of Adams-Stokes' syndrome is described in which bradycardia
occured from time to time for nearly six years.   An electrocardiographic
examination thirteen days before death revealed complete heart-block.
The patient died comatose : old inflammatory lesions were found which
seriously compromised but did not completely divide the main stem and
right branch of the auriculo-ventricular bundle.

AURICULAR FIBRILLATION AND COMPLETE HEART-BLOCK. A DESCRIPTION OF A CASE OF ADAMS-STOKES' SYNDROME, INCLUDING THE POST-MORTEM EXAMINATION.

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CLINICAL OBSERVATIONS.

THE history and the condition of the patient who forms the subject of this communication has been described in three previous articles. The original account is to be found in Mackenzie's paper.[8] More detailed accounts have been published by Lewis and Mack,[7] and by Lewis.[6]

It may be well briefly to recapitulate these reports.

M. M. was born in 1865 ; he contracted syphilis in 1887. In 1894, he had his first attack of syncope and had suffered from more or less prolonged attacks of loss of consciousness, sometimes accompanied by convulsions, up to the time when he was first examined. The first record of slow pulse rate dates from 1906, but his detailed history leaves little doubt that it had been present for a longer period.

He was seen by Dr. Mackenzie in November, 1908, when the first tracings were taken, and his pulse rate was then about 30 to the minute. He was under continuous observation from this time until the date of his death and was an inmate of a very large number of hospitals and infirmaries in London. The condition of the heart during the whole of the three years was almost constant. The ventricle generally beat quite regularly, at a rate of about 32 beats per minute, though from time to time the rhythm was disturbed by premature ventricular contractions. A total absence of any sign of co-ordinate auricular contraction throughout, and the replacement of these signs by those which, as we now know, characterise fibrillation of the auricle was a remarkable feature of the case.

The diagnostic features as they were summed up in the last report are as follows :—

1. *The evidence of complete heart-block.*

    A. A history of syphilis.

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* Working under the tenure of a Beit Memorial Research Fellowship.

B. The occurrence of fits accompanied by cessation of the ventricular action.

C. The persistence of a slow ventricular action in the intervals, at rates known to be characteristic of an independent ventricular rhythm.

D. The absence of compensatory pause after the premature ventricular beats.

2. *The evidence of auricular fibrillation.*

A. The complete absence of *a* waves in the jugular curves in scores of observations.

B. The complete absence of *P* variations in the electrocardiograms (Fig. 4).

C. The presence of the characteristic oscillations of auricular fibrillation in the electrocardiograms (Fig. 4)*; and, as may be now added, the occasional presence of rapid undulations in the venous curves during the diastoles.

D. The determination that the electric oscillations were maximal when leads were taken directly from the chest wall, the electrodes being fixed in the vicinity of the right auricle.

It was upon this evidence that the conclusion was based that the two conditions, heart-block and auricular fibrillation were present in one and the same patient.

In regard to the general course of the patient's illness between 1908 and 1911, it is only necessary to state that apart from slow and progressive weakening, there was no change, and that abundant records of the pulse and venous curve were taken in Dr. Mackenzie's clinic up till the day preceding death.

The nature of the terminal fits.

The fits observed during the last days of the patient's illness were not dissimilar to those previously recorded, with the exception that no movements of the veins of the neck were seen during the long periods of asystole which accompanied them. They have been described for us by Dr. Silberberg to whom we are indebted for the following observations.

" The attacks of unconsciousness and the mild convulsions commenced at 5 o'clock on the morning of July the 6th, 1911. They ceased at 9 a.m., but returned at 11 a.m., and continued at short intervals till 1 p.m. . Between 1 p.m. and 2.30 p.m. he was free from them. From this hour until death occurred (the morning of the 8th) there was a similar repetition of relapse and recovery."

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* For the figures, reference should be made to the original descriptions.

"The attacks were of varying duration ; lasting for a few seconds to twenty or thirty seconds. They were accompanied, one and all, by a lapse of the ventricular beats, readily observed at the prominent apex beat. The onset of unconsciousness was gradual, and the patient was aware of the impending attack, being conscious that his heart has temporarily ceased to beat. He became restless ; he groaned and uttered words of complaint. In a few seconds he could not be roused, the eyes rolled upwards and deviated to the right ; the pupils dilated fully, and the corneal reflex was lost. Cyanosis of the face, already present, deepened to lividity ; the breathing became stertorous and air was sucked in vigorously, his cheeks sinking deeply between his edentulous gums. Much flatus was passed. After twenty seconds of unconsciousness, epileptiform manifestations appeared ; the convulsions started in the face, the arms became rigid and spasmodic flexor movements appeared. The lower limbs showed no convulsive movements. A single beat of the heart, during the fit, lightened the degree of unconsciousness, two or three beats brought him to a dazed condition and, after a few more beats, he rapidly recovered, conversing rationally, though necessarily showing exhaustion. The first beat of the recovery was usually a weak one, the ensuing beats were more forcible. During the periods of comparative lucidity he complained of aching and sore feelings all over, more especially in the limbs. He was too feeble and exhausted to move. Pain, relieved by eructation, was present over the upper abdomen. On several occasions he vomited a pint or more of greenish fluid, an incident which seemed to afford relief."

The patient died in a fit on the morning of July the 8th. He became suddenly and deeply cyanosed, the face and arms showed the usual convulsive movements, but he failed to recover from the attack.

During the period of "status epilepticus," continuous tracings were taken by Dr. Silberberg from the apex beat. The rigidity of the arms and neck rendered further graphic record impossible ; the ventricular pulsations were the only prominent movements. The whole length of a long curve of 21 minutes duration is included in the accompanying diagram (Fig. 1), in which each beat has been accurately placed : (the error is nowhere greater than one-twentieth of a second). The rate at any point may be calculated from the vertical lines which are separated by two-second intervals. Two strips of the actual curve are published as examples of the observations (Fig. 2 and 3).

The events which are portrayed in this diagram are of very considerable interest. The usual rate of the rhythm of the ventricle for this patient was 32 per minute. This rhythm appears from time to time in the chart, and the rate is either 30 per minute or somewhat less, namely 27 ; thus it is seen over the whole of the lines, *h, j, k, l,* and *m,* and over the greater part of line *e.* The rhythm is not quite regular, for premature beats appear from time to time. These beats are separated from those which precede them by a second or a little more or less ; occasionally two or three premature beats

succeed each other (line *l* and line *d* directly after the pause), each following at about the same interval. From time to time they recur so frequently as to form a new rhythm, varying in rate from 60-80 per minute. It is the relation of these relative tachycardias to the periods of asystole which is so important. *The tachycardia, except where it is of brief duration, as in line " e," is invariably followed by a prolonged pause ; and none of the prolonged pauses of the curve occur except immediately at the termination of a period of relative tachycardia.*
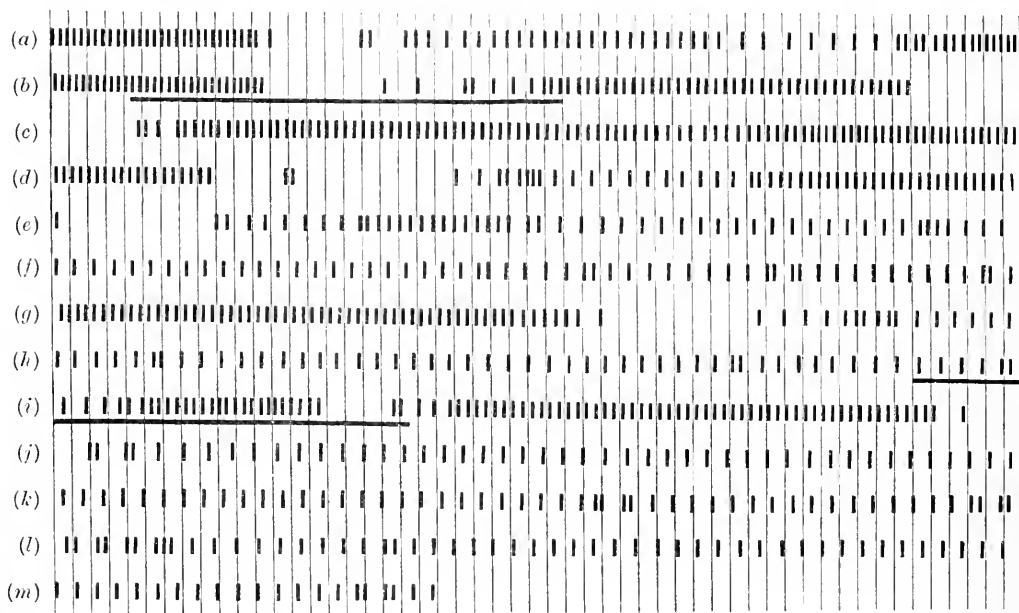
Fig. 1. A diagram compiled from a continuous curve of the apex beat, the duration of which was 21 minutes. The diagram reads from left to right, following consecutive lines. Each beat of the original curve has been charted on a large scale and the chart has been reduced subsequently photographically. The vertical lines are placed at two-second intervals. Two pieces of the original curve are reproduced in Fig. 2 and 3 ; the corresponding portions of the diagram are marked by means of heavy horizontal lines drawn beneath them. The relation of the (relative) tachycardial periods to the long asystolic intervals is very clearly shown.

The meaning of this phenomenon is quite clear. We have a clinical repetition of a phenomenon which has been studied experimentally and in detail by Erlanger and Hirschfelder.[4] When a slow ventricular rhythm is developed as a result of bundle section and a new and interrupting rhythm of faster rate is established, the new rhythm takes precedence to the old, and the latter passes into a condition of temporary abeyance. The cessation of the new rhythm is marked by a period during which physiological impulse formation in the ventricle is dormant and its awakening is gradual ; hence the long pause which follows the ending of the new rhythm. The nature of the fits, and the underlying cause in this patient, is consequently apparent. The long asystole or " stoppage " as Erlanger has termed it, is brought about
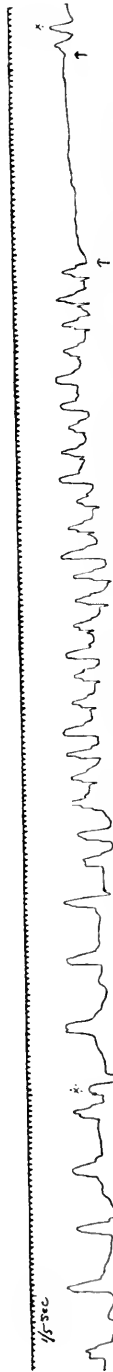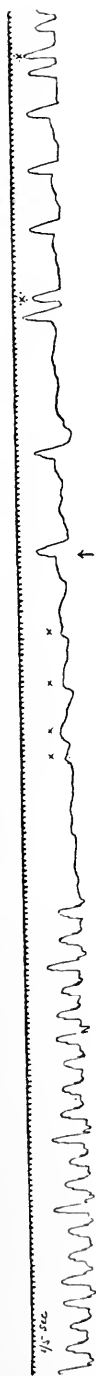
Fig. 2 and 3. Portions of the original curve from the apex beat. The time-marker is in one-fifth seconds.

Fig. 2 shows the termination of a period of relative tachycardia; it is followed by a pause of 13 seconds (the pause is interrupted by movements of the lever which were due to restlessness of the patient). The pause is followed by a slow but accelerating rhythm.

Fig. 3. Shows the commencement and termination of a short period of relative tachycardia; it commences in a premature beat and ends in a long pause of 8 seconds duration. Premature beats are marked by asterisks in the figures.

by an interference with the natural production of the idio-ventricular rhythm, as a result of the successive appearance of premature beats. In experiment the longest pause is generally followed by other pauses, which, though considerably longer than those which separate the beats of an established rhythm, are shorter than those which precede them. The same events are seen in this clinical case, though they are more irregular than are the experimental instances.

POST-MORTEM EXAMINATION.

The post-mortem was carried out by one of us at Mount Vernon Hospital on the 8th of July, 1911, a few hours after death. The body was that of a well developed and well nourished individual. Rigor mortis was present. There was slight œdema of the ankles. The conjunctivæ and skin had a yellowish tinge. An old and dense scar, 4 cm. in diameter, was noted above the right knee. Four other scars, each about 2 cm. in diameter and having a somewhat serrated margin, lay together over the left iliac crest. The external and internal jugular veins were a little dilated. The costal cartilages were not calcified.

Macroscopic examination.

The *tonsils* were fibrosed. The *tongue* and *palate* were normal. The mucous membranes of the *larynx* was yellow and thickened and showed some superficial petechiæ. The *trachea* contained a little frothy and bloodstained mucus. There were a number of dilated veins at the cardiac end of the

œsophagus. The *stomach* was more dilated than normal and its mucous membrane was deeply congested. The *intestines* and colon were not distended. The mucous membrane was injected.

The *pleurae.* On the right side, a transverse shelf of very strong adhesions, between diaphragm and parietal pleura, isolated the lower 12 cm. of the cavity. The lung lay entirely above it, but the space communicated with the main cavity by a small aperture in front. Isolated, thin but strong adhesions united the lung and parietal pleura ; they were thicker and more numerous at the apex and along the posterior margin. No fluid was found in the sac. On the left side and on a level with the heart, the lung was not visible from the front. The whole pleural space was obliterated by soft, spongy adhesions resembling connective tissue.

The *pericardium.* The pericardium was bound to the two pleural membranes, and to the chest wall in front, by soft adhesions of a character similar to those found in the left pleura. When fully exposed and viewed from the front, the pericardial sac and its contents filled the whole of the lower portion of the left pleural cavity. At the level of the fourth interspace, the right margin lay 7·5 cm. from the middle line. At the level of the sixth cartilage, the margin lay 11·5 cm. from the middle line. The apex lay in the anterior axillary line in the sixth interspace. The pericardial cavity was completely obliterated by abundant adhesions ; the two layers were fairly readily separable. The adhesions were firmer over the right auricle, and especially along the line of the sulcus terminalis, but the entire surface of the pericardium was roughened by the adhesions, which were old and dense. From the *A-V* groove to the apex along the anterior interventricular groove, the ventricle measured 16 cm. A similar measurement on the posterior surface was 12·5 cm.. The width of the heart along the posterior *A-V* groove was 13 cm.. The right ventricle occupied the greater part of the anterior surface.

The *heart.* The heart weighed 899 grammes. The surface of the heart presented a considerable increase of fat deposit. The fat around the auriculo ventricular groove was œdematous. There was little or no blood in the ventricles, but there was an excess of it in the great veins and auricles. The right auricle showed extreme dilatation, more especially the right auricular appendix. The cavity was about the size of a closed man's fist. The *tænia terminalis* in its upper extremity was hypertrophied, as were also the musculi pectinati, but the posterior wall of the right auricle was very thin. The endocardium was whiter than normal and seemed to be especially thickened below the orifice of the coronary sinus.

The tricuspid ring measured 13 cm. in circumference and readily admitted four fingers in line. The edges of the valve were slightly thickened but not hardened, and apart from slight matting together, showed no abnormality.

The right ventricle was slightly dilated. Its walls and trabeculæ were hypertrophied. The muscle was brown, soft, coarse and friable. The wall measured 9 mm. at the base at the right border, 4 mm. at the apex, and 6 mm.

at the conus arteriosus. On the trabeculæ and more especially at their origins and points of division there were irregularly shaped oval and linear thickenings of the endocardium. They were cream coloured, dense in consistency and circumscribed. These were elevated as much as 2 mm. above the surrounding surface and were from 1 to 2·5 cm. in length. On the endocardium of the conus arteriosus, 15 mm. from the pulmonary valve there were areas of a similar nature but more extensive, one measuring 20 and another 25 mm. in length. Their outline was very irregular. The cusps of the pulmonary valve were fenestrated and the *corpora-Arantii* were slightly thickened.

The left auricular appendix was bound down by adhesions and was noticeably smaller than the right. It measured 3·8 cm. as opposed to 8 cm. for the right, the measurement being made from the middle of the *tænia terminalis* to its apex. The wall of the auricle was dilated and moderately hypertrophied ; it measured 6 mm.. The endocardium was white and thick, but smooth. The mitral ring admitted three fingers in line. The edges of the mitral valve were thickened and smooth and not hardened. In the attached margins there were no calcareous deposits.

The wall of the left ventricle was dilated and hypertrophied and measured 17 mm. at the base, 22 mm. at the level of the papillary muscles and 9 mm. at the apex. The outflow tract below the root of the aorta was dilated. The wall of the left ventricle was thin at the left border, measuring only 5 mm.. 4 cm. above the apex. On this portion of the surface of the heart. the adhesions were very dense. The main branch of the coronary artery to this portion of the heart was not occluded. In places there were yellowish streaks in the muscle. Elsewhere there were numerous scars. The enlarged papillary muscles showed white subendothelial nebulæ. The endocardium was smooth on the whole, but moulded on the trabeculæ and also at their junctions, cream coloured plaques were found like those in the right ventricle. They were more numerous on the left side. The posterior aspect of the posterior papillary muscle was entirely encased by such material. In the outflow tract, directly under the anterior portion of the membranous septum. a similar thickening was found, elevated 2 mm. above the level of the endo-cardium, and measuring 1 × 2 cm.. The other plaques of similar nature varied in length from a few millimetres to several centimetres. No calcareous deposits could be felt in or about the septum membranaceum. At the upper portion of the left ventricle, at the level of the *A-V* ring and at the right half of the cavity was an *intracardial aneurysm.* Its exact position (Fig. 5). was to the right of and behind the junction of the two flaps of the mitral valve and consequently to the left of and below the origin of the aortic valve, more especially its right posterior cusp. The aneurysm was shaped like a portion of a sphere. Its diameter was 33 mm.. The posterior wall of the aneurysm was formed by the posterior wall of the ventricle, and its level was that of the coronary sinus. The coronary sinus was compressed from before backwards but its lumen was not compromised, while the branches of the

coronary artery, though small, were not occluded. The right wall of the aneurysm was formed by the septum between the left ventricle and right auricle and corresponded in part to the insertion of the mesial flap of the tricuspid valve. The wall of the aneurysm was calcareous but smooth and showed no thrombi. Pressure in the aneurysm was directed backwards, upwards and to the right and was exerted on the end and the opening of the coronary sinus, and also on the septum between the two sides of the heart so that this was protruded into the cavity of the right auricle (see Fig. 5). The involved area corresponded, when seen from the right auricle, to the wall lying between the opening of the coronary sinus and the septum membranaceum. It is just in this situation that the auriculo-ventricular node and the beginning of conduction system is usually found. It was presumed that the aneurysm might have damaged these structures. Examination of Fig. 8 will show that this was not the case.

The lunulæ of the aortic valve were thickened and so were the *corpora Arantii*, but the valve presented no other abnormality. There was some atheroma in the sinuses of the *Valsalva*. Atheroma and athero-sclerotic patches were found along the course of the coronary arteries. These did not seriously narrow the lumina of the vessels anywhere. The foramen ovale was closed.

The *arteries*. The pulmonary artery showed occasional atheromatous patches and was pinkish-yellow in colour. The thoracic aorta was bile-stained, the endothelium seemed to be a little œdematous and there were scattered patches of atheroma. The abdominal aorta was extensively degenerated. Atheroma was advanced ; œdema and ulceration were present. The coronary arteries presented little thickening ; the coronary sinus and the cavities of the heart were free of ante-mortem clot.

The *lungs*. The right lung weighed 560 grammes, the left 525. The tissue was deeply pigmented, emphysematous and a little œdematous. Otherwise these organs were normal. The bronchial lymph nodes were black. Neither these nor the mediastinal nodes were enlarged or fibrosed.

The *liver* weighed 1,236 grammes. It was small and very hard. A number of firm, isolated adhesions united it to the diaphragm. The surface was irregular and showed a mild degree of hobnailing. One or two large superficial scars were present. The section was mottled red and greenish-yellow. The red areas were depressed. Fine, pink trabeculæ of fibrous tissue were clearly visible throughout large areas of the organ. The tissue was very tough. Glisson's capsules seemed more fibrous than usual. The liver appeared to be fatty, fibrous, congested and somewhat bile stained. The gall bladder was small and the wall was thick.

The *spleen* weighed 640 grammes. The surface was adherent to the diaphragm in several places. A number of small, irregularly shaped, cream-white masses were present on the surface and projected from it. The organ retained its shape. The section was dark, the tissue tough ; the Malpighian capsules were not prominent. There seemed to be an increase of fibrous tissue.

The *pancreas* was larger than normal and consisted chiefly of mottled pink and yellow areas, in which the gland substance could be traced only from place to place.

The *kidneys* weighed 176 and 192 grammes respectively. The capsules were non-adherent. Apart from the conspicuousness of the glomeruli and slight general congestion and increased firmness, they seemed to be normal.

The *suprarenals* appeared to be normal. The cortex was dark brown, and the medullary substance light grey.

The *testicles*. Both tunicæ vaginales contained about a drachm of yellow fluid. On the right side the testicle was normal, and there was a varicocœle. The left testicle was small and fibrosed.

The *peritoneum* was smooth. There was about a half-pint of yellow fluid in the cavity.

The *brain*. The calvarium was normal. The pia-arachnoid membrane was œdematous; the superficial veins were congested. The basal and cortical arteries were normal. The brain showed no abnormality on section. The venous sinuses were empty.

The *vagus and sympathetic nerves* presented no abnormality.

Microscopic examination.

All the pieces excised for microscopic examination were fixed in Müller-formol (9 : 1). The heart, medulla oblongata, pons and vagus nerves were fixed in the same fluid. The technique of examination of the heart was the same as that used and already described in this *Journal*.[1] On account of the difficulty which would have been experienced in cutting sections of the septum of the heart with the aneurysm in place, it was decided to shell out this structure. This proceeding was accomplished successfully. No incisions were necessary; blunt dissection sufficed to enucleate it in one piece. The description given below (see Fig. 5) will show that no injury whatever was sustained by the structures of interest in this study. The following tissues were excised for examination :—

    (1) The cavo-auricular junction, bearing the sino-auricular node.

    (2) A portion of the septum between the two halves of the heart, bearing the auriculo-ventricular node, main stem and branches.

    (3) A piece of the left ventricle.

    (4) Four pieces of the aorta, two thoracic and two abdominal.

    (5) Two pieces of the liver.

    (6) A piece of the pancreas.

    (7) A piece of the spleen.

    (8) Two pieces of the kidney.

    (9) The medulla oblongata and pons Varolii.

    (10) The two vagus nerves.

The *cavo-auricular junction, bearing the sino auricular node.*   A piece of the superior vena cava was left attached so that Wenckebach's bundle could be examined.   Apart from the changes which occurred in the cardiac muscle fibres in this case, no pathological lesions were found.   The amount of connective tissue was not greater than elsewhere and there was no evidence of acute inflammation.   The muscle fibres throughout those portions of the heart examined were much larger than normal.   There was no fragmentation of the muscle and no granular degeneration.   The transverse striation was clear and the nuclei well stained.   In many of the muscle fibres there was an unusually large space about the nucleus which was clear of muscle fibrils, so that they resembled Purkinje cells.   They had no definite arrangement, and were so scattered as to make it impossible to regard them as forming a system.   The spaces about the nuclei contained no pigment.   The nuclei themselves varied very much in size and shape, but for the most part they were much larger than normal.   Their margins were usually irregular and the distribution of chromatin was uneven.   Here, as elsewhere throughout the heart, connective tissue of a loose areolar nature was increased between the fibres and numerous scars of connective tissue were found.   The smaller blood vessels were abnormal.   The adventitia was but little thickened but there was thickening of the muscle of the media.   The position of the internal elastic membrane showed an increased amount of connective tissue which sometimes extended into the intima.   In a few places, loose connective tissue was seen invading the media from the adventitia.   Vacuoles appeared frequently in the muscle fibres of the vessels.   The intima was hyperplastic in many places, and the lumen often seriously reduced in diameter.   A few small vessels were found to be occluded and others presented but a slit-like channel.   The elastic tissue throughout the heart stained poorly or not at all, and was in marked contrast to that found in the kidney of the same case, which was used as a control.

The sino-auricular node was seen at a level below that at which the cavo-auricular junction was formed.   The angle of junction lay, in fact, 3 mm. above the upper extremity of the node.*   The node could not be said to lie in the wall of the superior vena cava.   At the anatomical junction between the superior vena cava and the auricle, there was complete separation of the muscular systems of both by fat and by some connective tissue.   It was in this fatty tissue that the node was first seen, lying much nearer the vena cava than the auricle but quite separate from it.   From its upper extremity to its end, it measured 21·55 mm., the measurement being computed from the thickness of the sections multiplied by the number in which it was found.   The upper extremity of the node lay, as has been said, nearer the superior vena cava, while a little lower down it was situated nearer the auricular muscle.   It was found close to the pericardium throughout, except

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* Koch[5] has shown that in the hearts of dogs, an extension of the sino-auricular node reaches 2 mm. upward on the wall of the superior vena cava, but that the node can be recognised 0·75 to 1 mm. above the cavo-auricular angle.

at its upper extremity. Here it was 3·5 mm. from the surface, but a little lower (1·5 mm.), it was 1·5 mm. deep and maintained this depth (0·75 to 1·5 mm.) throughout its extent. The shape of the node varied constantly in its course. In its highest level it was roughly triangular, the apex of the triangle pointing toward the pericardium. A little further down, the node was circular (Fig. 6). But the greater portion of it (66%) had an elongated shape, the long axis in cross section being parallel to the pericardium (Fig. 7). The greatest length of this long axis was 5·5 mm. and its width at the corresponding level varied from 1·0 to 0·25 (See Table I).

TABLE I.

		Depth.		Length. Width
Slide 122	.. ..	3·5 mm.	.. ..	0·75 × 1·5 mm.
,, 134	.. ..	2·0 mm.	.. ..	1·00 × 3·0 mm.
,, 141	.. ..	mm.	.. ..	1·00 × 2·0 mm.
,, 155	.. ..	1·5 mm.	.. ..	2·00 × 2·0 mm.
,, 181	.. ..	1·0 mm.	.. ..	2·00 × 1·0 mm.
,, 199	.. ..	1·0 mm.	.. ..	2·00 × 1·0 m.m.
,, 226	.. ..	1·0 mm.	.. ..	1·50 × 1·5 mm.
,, 257	.. ..	1·0 mm.	.. ..	1·50 × 1·5 mm.
,, 284	.. ..	1·0 mm.	.. ..	2·50 × 1·0 mm.
,, 292	.. ..	0·75 mm.	.. ..	3·00 × 1·0 mm.
,, 310	.. ..	0·75 mm.	.. ..	4·50 × 0·5 mm.
,, 324	.. ..	0·75 mm.	.. ..	5·00 × 0·5 mm.
,, 344	.. ..	0·75 mm.	.. ..	5·50 × 0·5 mm.
,, 351	.. ..	1·00 mm.	.. ..	5·50 mm.
,, 358	.. ..	1·00 mm.	.. ..	3·0 × 0·25 mm.
,, 364	.. ..	1·00 mm.	.. ..	3·5 × 0·5 mm.
,, 384	.. ..	1·25 mm.	.. ..	3·0 × 0·25 mm.
,, 393	.. ..	1·50 mm.	.. ..	2·25 × 0·25 mm.
,, 402	.. ..		.. ..	1·50 mm.
,, 416	.. ..	1·50 mm.	.. ..	0·50 mm.

The upper third of the node was entirely destroyed by connective tissue. This was dense and probably old (Fig. 6). Fat tissue occupied the area at the sides of the node, between it and the pericardium, and was also found within its structure. Except in one or two places, where there were round cells, there was no evidence of a recent or acute inflammation. Below this level, that is, in the lower two thirds, muscle tissue appeared in the node and rapidly increased in amount, but the amount of connective tissue was probably always more than normal (Fig. 7). The increasing amount of muscle tissue occurred at the anterior portion of the node, while the posterior portion remained quite sclerosed. The node was at almost every level in direct relation with nerve trunks. Ganglia were found, as were also nerves which contained ganglion cells. About some of these there was dense connective tissue. The node contained an artery and in some sections two. In some parts of its course, the artery showed a distinct endarteritis. A small artery at one level was entirely occluded and canalized.

The auriculo-ventricular system. A block of tissue, including the interauricular and interventricular septum, was excised. The upper margin ran parallel with the upper edges of the aortic cusps, the lower margin was

parallel with this, two to three centimetres below the membranous septum ; the anterior margin was at the anterior extremity of the septum, and the posterior margin was the posterior wall of the heart itself. The sections were cut parallel with the upper margin. The entire site of the aneurysm already described was included in the block. The bed of the aneurysm was found to be a connective tissue structure, of a dense fibrous nature, which looked old. In a few places near the wall there were collections of lymphocytes. This was the only evidence of recent or acute inflammation. The bed of the aneurysm, which was also the inter-auricular septum (see Fig. 5 and 8), was very much thinned, convex towards the right auricle and contained no muscular tissue. The entire septum was consequently converted into a wall composed of fibrous tissue. Examination showed that the removal of the calcareous portion of the aneurysmal sac had involved the loss of no structure necessary for this study. The septum contained no muscular structures between the coronary sinus behind and the central fibrous body in front. Muscle fibres survived above the level of the aneurysm rather high above the auriculo-ventricular groove, but they did not descend to the auriculo-ventricular node. There was consequently no connection between the auricular muscle and the node ; the auriculo-nodal junction did not exist. Except for the muscle tissue of the auriculo-ventricular system, to be described presently, the entire interauricular and interventricular septum in the neighbourhood of the aneurysm, the central fibrous body and the septum membranaceum were replaced by dense old connective tissue, poor in nuclei ; and in some places, notably in the posterior wall of the heart and at the root of the aorta, by fatty tissue. That portion of the interventricular septum in which the upper portions of the right and left branches of the conducting system are usually found, was also replaced, for 2 cm. anterior to the membranous septum, by connective tissue of the kind described. Muscle tissue was seen only in the lower parts of the block. In the sections the coronary sinus was seen to be compressed from before backwards. That wall of the sinus which was directed toward the cavity of the auricle contained a thick layer of loose connective tissue. The cardiac muscle tissue in this situation was thinned and was infiltrated with large amounts of dense connective tissue. A number of vessels were compressed and showed advanced endarteritis to the point of occlusion.

The auriculo-nodal junction, as has been said, did not exist. The node was, however, a well developed structure and showed the familiar interlacing arrangement. It followed the usual appearance of this structure also in the number, shape and size of the nuclei, the fineness of the fibres and the arrangement of the fibrous tissue. It was a normal node. At one portion a few small, dense masses of connective tissue were present but they did not appear sufficient in size or number to be considered pathological. The artery to the node appeared in the lower regions only. Its adventitia was thick and there was much connective tissue in the intima. At still lower levels the lumen was contracted on account of endarteritis. Passing forward from the

node (Fig. 8), the main stem of the *A-V* bundle progressed normally through the septum membranaceum for about 2 mm. when it ceased suddenly in the dense connective tissue of the septum already described. About 3 mm. farther along, the main stem was again identified. A hiatus of about 3 mm. was thus caused between the *A-V* node and the main stem, in the upper portion ; of about 7 mm. at the lower ; and of 12 mm. at the lowest level. The main stem was then followed through the septum membranaceum about 3 mm. Its anterior end was terminated by the dense connective tissue of which the septum ventriculorum was composed. The division of the main stem into the right and left branches was nowhere seen. This portion of the system, as well as the origin of the branches, was completely destroyed by the sclerotic process. The right branch was not identified at lower levels, but the left branch was clearly seen 6 mm. below the point at which the main stem disappeared. The failure to identify the right branch was due, no doubt, to the fact that the right half of the interventricular septum was sclerotic at levels lower than the left half. The left branch of the bundle did not partake of the hypertrophy of the rest of the heart. The nuclei of the conduction fibres were slightly irregular but the change from the normal shape and structures was much less than that seen in the intrinsic cardiac muscle. The distinctiveness of the nuclei of the conducting muscle was recognised here as well as in other hearts. The endocardium which lay over the left branch was especially thick, the thickening being due to fibrous changes in the lining membrane of the heart. The smooth muscle of the endocardium showed a normal development.

The *aorta*. The cusps of the sinuses of *Valsalva* were sclerotic, and this sclerosis involved the junction of the cusps especially. The aortic wall contained an increased amount of connective tissue. The thoracic aorta showed moderate thickening of the intima, the elastic tissue of which was hyperplastic. The medial layer was practically normal. Occasionally large plaques of the intima occurred, which showed degenerated and œdematous loose fibrillar connective tissue. They contained no calcium, cholesterin, or debris. The abdominal aorta showed areas where there were lymphocytic and rarely leucocytic collections in the intima. In a few places the media where it adjoined the intima was degenerated. Here the nuclei were not stained and the tissue looked hyaline. Elsewhere the media showed an increased amount of connective tissue. The intima was unequally thickened and showed distinct plaques. The plaques were hyaline, non-cellular, and in a few, large collections of needle-like vacuoles were seen, which in the recent state had been occupied by cholesterin crystals. In other portions of the intima there were cellular elements, lymphocytes, leucocytes and plasma cells. There was no deposit of calcium. Another section showed necrotic plaques which were in a pre-ulcerative stage. Here the degenerative changes in the media were more advanced, in that the nuclei did not stain and the tissue had assumed a hyaline appearance.

The *liver.* The capsule was very thick and in places shaggy. The thickening was for the most part due to an increased amount of fibrillar connective tissue, of normal appearance. In other places the thickening was due either to destruction or to partial atrophy of the underlying liver cells. The central veins were dilated, the surrounding liver cells were atrophic, and in many there was advanced fatty degeneration. A number of these cells showed brown pigment. In these areas a number of acini were compressed. The capsules of Glisson were normal.

The *pancreas.* There was increased interstitial fatty tissue and also some increase in the amount of connective tissue.

The *spleen.* The capsule was much thickened by dense masses of connective tissue. The substance of the gland was congested ; and there appeared to be more than the normal amount of lymphatic tissue in it.

The *kidneys.* The glomeruli were distinctly more congested than were other parts of the organ. Adjoining the capsule, there were a number of small areas containing lymphocytes and others where there was an increase of connective tissue. The vessels were normal. There was a hyperplasia of the internal elastic membrane, probably normal at this period of life.

The *medulla oblongata* showed no abnormality. It was examined in serial sections.

The *right vagus nerve* showed no abnormality. Many ganglia were seen incorporated in its course. A small nerve (presumably the sympathetic) was seen running parallel with the vagus, into the interstitial tissue of which a hæmorrhage had taken place. The *left vagus* was like the right and in the section a small nerve containing a hæmorrhage was also seen.

Summary.—(1) The medulla oblongata showed no gross lesion. The vagus nerves were normal, but parallel with each nerve there was a small one containing a hæmorrhage. (2) The heart was hypertrophied in all its cavities. There was an aneurysm in the right upper portion of the left ventricle. There was partial sclerosis of the septum ventriculorum and complete sclerosis of the septum membranaceum. The myocardium contained numerous scars. There was practically no acute inflammation. The sino-auricular node was in part destroyed, being replaced by connective tissue. The main stem of the auriculo-ventricular bundle was divided from the auriculo-ventricular node by sclerotic tissue ; and the distal end of the main stem, its point of division and the upper parts of both branches were destroyed by the same process. The arteries of the heart showed hypertrophy of the media, degeneration of their muscle fibres, and hyperplasia of the intima causing either partial (the more common lesion) or complete obliteration of the lumina. The aorta showed athero-sclerosis. (3) The liver showed chronic congestion, as did also the spleen, pancreas and kidneys.

Relation of lesions and heart mechanism.

We do not propose to discuss the question of auricular fibrillation and its morbid anatomy at any length. The findings in this case, the partial destruction of the sino-auricular node and the scattered fibrosis in the auricle, conform with those which have been found by a number of other writers.

The case was remarkable clinically for the presence of definite signs of auricular fibrillation, while *the ventricular action instead of being rapid and irregular*, as is usual in such cases, was *slow and regular*. The opinion was held, and is still held, that a regular action of the ventricle is never associated with auricular fibrillation, except when complete functional dissociation of auricle and ventricle, so far as conduction is concerned, is present ; and it was felt that as the ventricular action was persistently slow and regular, a lesion accounting for this action would be found, which was comparable to the lesions discovered at autopsy when ordinary dissociation of auricular and ventricular rhythms occurs. This expectation has been fully realised by the examination of the heart in this unique case. Complete division of the junctional system occurred at two levels at least. The post-mortem findings confirm the conclusion that if, in a case of auricular fibrillation, the action of the ventricle is regular, there is complete functional separation of the two chambers, so far as the conduction of impulses is concerned. The case is, so far as we know, the only one of its kind which has been recorded.

But there is another matter in connection with it of considerable interest. The post-mortem examination shows a lesion at the division of the bundle, and *destruction of the upper ends of both the branches.* Now when there is a single lesion of the main stem, the electrocardiogram of the ventricle retains its original form, consisting of the normal Q, R, S and T, or R, S

Fig. 4. (Reproduced from *Heart*, Vol. 1, p. 306, Fig. 18). An electrocardiogram, showing auricular fibrillation and the slow and peculiar ventricular beats which are considered to be associated with the action of a heart, in which both bundle branches have been destroyed. Note the duration of S. The time marker is in one-fifth seconds.

and T variations. When one or other branch is divided, anomalous electrocardiograms are produced, which as Eppinger, Rothberger and Stoerk[2 & 3] have shown, are distinctive of the lesions in question. In this clinical instance both branches were destroyed and it might be anticipated that, as a result, the ventricular electrocardiogram would be considerably modified. One of the original curves is shown in Fig. 4; it was taken

from lead *II*.   Two ventricular beats are seen ;   *R* is small, *S* is deep and *T* is tall, but the chief feature of the curve is *the breadth of* " *S.*"   The   total duration, from the commencement of *R* to the end of *S* is approximately one-fifth of a second.

There is but one published electrocardiogram from an experiment in which both bundle branches had been cut.   It is given by Eppinger and Rothberger[2] (Fig. 8 of their paper).   The curve is almost identical with that now published ;   *R* is short, *S* is deep and *T* is full ; but again the chief feature is the duration of *S*.   The clinical and pathological observations are thus in the most complete accord.   It seems from the comparison that division of both branches of the bundle may be diagnosed clinically.

SUMMARY.

1.   The   pathological report of a patient previously described as exhibiting auricular fibrillation and complete heart-block is now given. Complete division of the bundle was found, and lesions compatible with auricular fibrillation were seen.

2.   The observations support a former conclusion that, when auricular fibrillation is associated clinically with a regular action of the ventricle, impulse conduction from auricle to ventricle is in abeyance.

3.   A lesion is also described which divided both branches from the main stem of the bundle and from each other ;   the electrocardiograms were of the form seen by Eppinger and Rothberger to follow a similar experimental lesion.

4.   The lesions in the heart were of syphilitic origin and included a septal aneurism pointing from the left towards the right side, *i.e.*, from the direction of greater to that of lesser pressure.

5.   The patient was the subject of syncopal attacks.   The nature of the heart pauses, responsible for the attacks, has been shown.   They followed periods of relative tachycardia, resulting from new impulse formation in the ventricle.   This observation is exactly parallel to the experimental findings of Erlanger and Hirschfelder.

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Fig. 7.

SINUS OF VALSALVA

LEFT VENTRICLE

CENTRAL FIBROUS BODY

RIGHT CORONARY
VALVE OF AORTA

SEPTUM MEMBRANACEUM

A.V. NODE

INTERAURICULAR
SEPTUM

AV BUNDLE
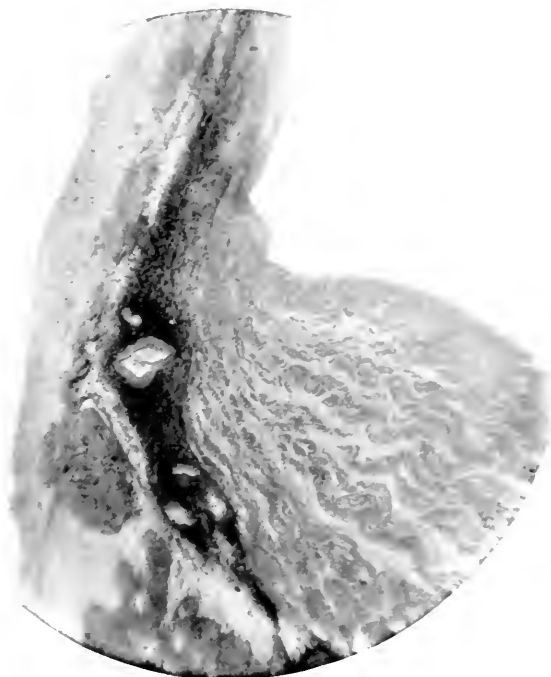
Fig. 8.

Fig. 5.

Fig. 7.
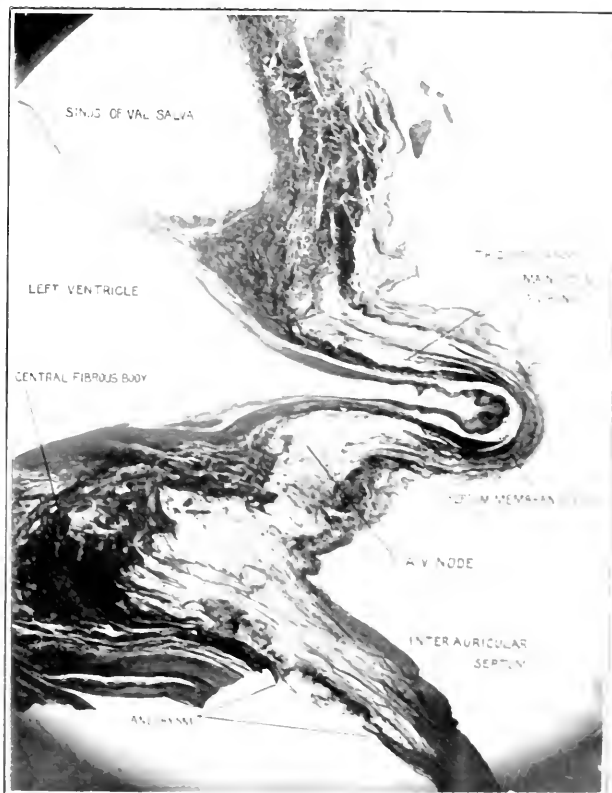
Fig. 5. (× 17). Slide 132. Photograph of section to show the relation of the portions described.

Fig. 6. (× 22). Microphotograph of the sino-auricular node. Sclerosis of the node and fatty tissue within its structure, and between it and the pericardium, are shown. Its shape is oval; it measures 2 · 1 mm., and lies 1 mm. from the pericardium.

Fig. 7. (× 11). Slide 328. Microphotograph of the sino-auricular node, showing the elongated shape at a lower level. The node here is 5·5 mm. long, 0·5 mm. wide and lies 0·75 mm. from the pericardium.

Fig. 8. (× 5). Microphotograph showing the septum of the heart. Above is seen the cusp and sinus of Valsalva of the right anterior cusp; in the centre is the septum membranaceum. This portion of the heart was bent in fixation. The largest portion shown is the central fibrous body. At the bottom is the rough surface which was the bed of the aneurysm described in the text. The auriculo-ventricular node is shown to the right of the central fibrous body. The bent portion which represents the septum membranaceum is sclerosed and forms the barrier between the node and the main stem, seen in the upper arm of the bent septum. The anterior end of the main stem is seen to be terminated by the fibrous tissue of the septum.
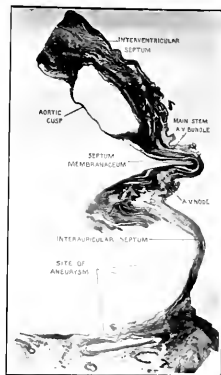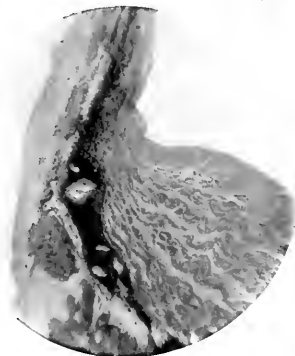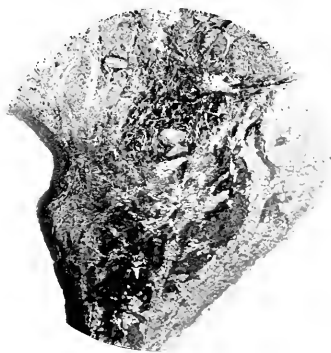
Fig. 6.
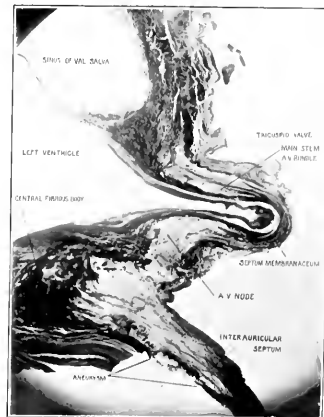
Fig. 8.

THE RÔLE OF THE GASTRIC JUICE IN THE PATHOLOGY OF GASTRIC ULCER.

(With Lantern Demonstration.)

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THE part played by the gastric juice in producing and maintaining gastric ulceration is a useful subject for discussion, since a knowledge of this aspect of the question is particularly useful to the practitioner of medicine in the treatment of the disease.

It is quite impossible to obtain an exact idea of the influence of the gastric juice in this connexion by the study of human pathology alone, and the diversity of the opinions which have been expressed at various times is a proof of this statement. The chief reason for this is that in any given case of gastric ulcer the pathological processes present involve so many factors that it is quite impossible to assign to each its proper significance and value. By experiments on animals we can isolate these factors and study the influence of each separately.

I propose, therefore, to give you very briefly the results of an experimental inquiry into this question, which have been published separately at intervals during the past few years.

The method by which I have produced these experimental ulcers in the first instance is one which I described some years ago, and consists in the injection into the animal of a toxic serum which has the property of attacking its gastric mucous membrane and producing gastric ulcers. Whether the serum reaches the stomach through the general blood stream or is injected directly between the coats of the stomach does not matter. In either case ulceration is produced, but in the former general toxic symptoms result, and the animal may die, whilst in the latter only slight symptoms result, and an ulcer is formed at the site of injection. The method of injection into the stomach wall is, therefore, the most convenient to employ when one is studying the healing of the ulcers, because an ulcer can be produced in any position in the stomach, and of any size, without the animal

[613/12]

suffering more than a few hours' inconvenience from the general toxic effects of the serum. The serum is that of an animal which has been immunized by repeated injections of the gastric cells of another animal.

The two animals in which ulcers have been produced in these experiments are the guinea-pig and the cat—in the former by injection of immune serum obtained from the rabbit, and in the latter by injection of serum obtained from the goat. The lesions produced by this serum are necrotic in character. The necrosis involves the mucous membrane, and the result is an ulcer extending to various depths. It may only involve the submucous tissue, or may reach to the peritoneum, and perforation result.

The part played by gastric juice in the formation of these ulcers I have found to be a very important one. In fact, if the gastric juice be temporarily put out of action, ulceration fails to appear at all, although the animal dies from the general poisonous effects of the serum.

In order to demonstrate this, two guinea-pigs of the same weight are injected via the peritoneum with the same dose of serum. A solution of sodium bicarbonate is introduced into the stomach of one of them in order to put the gastric juice out of action whilst the poison is acting. If a lethal dose of the serum has been injected both animals will die within twelve hours. The stomach contents of the animal which has received the soda will be alkaline in reaction, and its mucous membrane be quite normal to the naked eye, whilst the stomach contents of the other will be acid in reaction, and the mucous membrane will show the usual black patches of necrosis and ulcers. Hence the serum does not produce the necrosis of the gastric cells, but brings about some change in them which renders them susceptible to the action of the gastric juice. The process is, therefore, one of digestion of the gastric mucous membrane by the gastric secretion owing to some change which has occurred in it. What that change is I cannot say, because no microscopic alteration can be seen in the cells before they are digested.

It does not appear to me to be due to the removal of any specific resisting power possessed by the gastric cells, because I have shown that other blood poisons, which cannot have any influence in this direction, are able to likewise bring about self-digestion. It is undoubtedly a question of the infliction of a certain amount of injury upon the cells, and necrosis and ulceration are produced merely because the cells happen to be exposed to the action of a digestive fluid.

The establishment of this principle is of great importance, because it demonstrates how blood poisons, of which we are at present ignorant, may produce their effects upon the stomach. We know that one important cause of gastric ulcer in the human being is bacterial invasion of the body either as a septicaemia or from some local, and perhaps unsuspected, focus of infection. The organisms, or their poisons, gain entrance to the gastric mucous membrane by the blood stream. It is not neces-

sary for them to kill the gastric cells, but if a certain amount of damage is inflicted upon the latter, the gastric juice is then able to complete the death of the tissue and so produce an ulcer. This explains why these bacterial ulcers are found so much more often in the stomach than in other parts of the body. The same remarks apply to the ulcers found in other intoxications of the body—as, for example, in burns. In almost half the cases such toxic ulcers are single, and many instances are on record of the transformation of such acute ulcers into chronic ones.

This action of poisons circulating in the blood suggests that certain substances introduced into the cavity of the stomach may produce a similar effect, and we already have one protoplasmic poison present in the gastric juice—namely, hydrochloric acid. The effects of hyperacidity of the gastric juice are interesting. The amount of HCl present in the guinea-pig's stomach contents is the same as in man—namely, about 0.2 per cent. One may introduce into the guinea-pig's stomach solutions of HCl of any strength up to 0.7 and 0.9 per cent., depending on the weight of the animal, and no lesion is produced, but with strengths above these necrosis and ulceration are produced. In the human being the percentage of HCl never reaches these limits, and therefore hyperacidity alone, such as is found in disease, is unable to produce ulcer, but I have been able to show that it is *potentially* able to do so, and that in the presence of another poison a hyperacid gastric juice will do more damage to the stomach wall than one of normal acidity. In order to demonstrate this two guinea-pigs of the same weight are injected via the peritoneum with the same dose of serum. A solution of HCl, of any strength beween 0.3 and 0.7 per cent.—in other words an innocuous fluid—is introduced into the stomach of one of them at the same time.

In the twenty-two experiments of this series which I have done the result was in all cases the same. The gastric lesions in the stomach of the animal which had received the HCl were much more marked than those in that of the control animal. So that HCl, of such strengths as may be found in the condition of hyperacidity in disease, is able to act as a poison for the gastric cells. I have found precisely the same results to occur in the case of other acids, including biliary acids. The results with acetic acid are interesting, because vinegar, which is sometimes largely consumed by a certain class of individual, contains 4 per cent. glacial acetic acid. I found a 0.5 per cent. solution, or one of any strength above this, to markedly increase the lesions produced by gastrotoxin. Lactic acid, on the other hand, which is formed by bacterial fermentation in the stomach under certain conditions, is not so potent in this respect, but 3 or 4 per cent. solutions will cause an increase of the lesions.

The rapidity of formation of an ulcer of the stomach varies according to the activity of the gastric juice. After a meal of 100 to 120 grams of meat the cat's stomach is

usually not empty till a period of about twelve hours has elapsed, whilst after a meal of 6 oz. of milk it is empty in three hours. The stomach of a 3,000-gram cat will hold, when fully distended, a little over half a pint, but the animal will only drink about 6 oz. at once.

I conducted a series of experiments in which half the animals were fed on meat and half on milk, an ulcer being produced in each cat by local injection of immune goat's serum. When the animal is fed on a meat diet, so that the walls of the stomach are exposed to the prolonged action of the gastric juice, the slough is rapidly formed, and has separated by the fourth day in most cases, a clean ulcer resulting. In the case of animals fed on milk, however, the period of formation of the ulcer is longer. In two cases the slough had not separated on the seventh day, and in two other animals, killed on the eighth and eleventh days respectively, a small slough was still adherent to the centre of the ulcer. The same result is seen in the case of fasting cats. When the stomach is empty the ulcer may not appear at all, or, if it does, it is quite superficial. We see therefore that, when all the conditions necessary for the production of ulcer are present, the rate of formation of such an ulcer and also its extent are largely dependent upon the condition of the gastric juice. In the human being acute ulcer is initiated in several ways, but in all cases, by the action of the gastric juice, the different lesions are eventually converted into precisely the same kind of ulcer, so that in most cases it is impossible to say how the ulcer took its origin.

I now pass to a consideration of the influence of the gastric juice upon the healing of experimental ulcers.

The healing of acute ulcer was first studied in 40 guinea-pigs and 21 cats on a normal diet, and I found that in all cases healing occurred in about three weeks, the exact time depending on the size of the ulcer.

In order to test the effect of hyperacidity of the gastric juice, ulcers were produced in 24 guinea-pigs. Half the animals were put on a normal diet and half on an acid diet, which consisted of food soaked in 0.6 per cent. HCl. I had previously found that by feeding the animals on such a diet it was possible to keep the stomach contents permanently hyperacid to the extent of about 0.27, or 0.3 per cent. This investigation showed that the ulcers in the animals fed on an acid diet passed through precisely the same stages as those of the animals fed on a normal diet, and that they healed up in the same time. The same results were obtained in a series of cases in which a diminution of the acidity of the stomach contents was present. Half the animals were fed on food soaked in a 4 per cent. solution of sodium bicarbonate, which effects this result, and half were fed on a normal diet. In each case healing occurred in practically the same period of time.

When the motor power of the stomach is interfered with, however, a definite delay in the healing of the ulcer occurs. Pyloric stenosis was produced in cats by con-

stricting the first part of the duodenum with a piece of rubber tubing.

Retention of food in the stomach was thus produced and consequent dilatation of the organ. Ulcers were produced in a series of cats having pyloric stenosis, and in normal cats as controls. I found that motor insufficiency of the stomach definitely delayed the healing of the ulcers for at least twice the normal time.

The delay in the healing occurred during the early stages, before the single layer of cells, which eventually develops into glands, had completely covered the base. The cause of this delay was not due to a fault in the epithelium but to necrosis of the connective tissue base of the ulcer—so that the epithelial cells had no granulation tissue over which to grow—and also to excessive formation of fibrous tissue in the base, the young glands having no cellular stroma in which to proliferate. These conditions were due to the retention of food in the stomach, which allowed of a prolonged action of the gastric juice upon the connective tissue base of the ulcer.

The time of healing of acute ulcer also depends upon the quality of the food, for the same reason. We have seen that meat is retained in the stomach longer than milk, and that it produces a greater flow of gastric juice. In a series of experiments in which half the animals were fed on meat and half on milk, I found that the ulcers of those fed on milk healed up more rapidly than those of the meat-fed animals.

The delay occurred in the early stages of healing and was due to the condition of the base of the ulcer. When once the base was covered with a single layer of epithelial cells so that it was thus protected from the action of the gastric juice, the further changes in this layer progressed at a rapid rate.

The glands of this regenerated mucous membrane were more irregular and not so perfectly formed as in the condition of normal healing, because of the excessive formation of fibrous tissue in the base, resulting from the irritation of the gastric juice.

In the treatment of a case of gastric ulcer, therefore, the acidity of the stomach contents should be kept low by the administration of· alkalis. The diet should be free from irritants, and should consist of foodstuffs which remain only a short time in the stomach and excite only a moderate flow of gastric juice. If there is present dilatation of the stomach and retention of food owing to muscular insufficiency, which resists medical treatment, or pyloric stenosis, gastro-enterostomy should be performed.

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A NOTE UPON

THE COMPLETE REMOVAL OF PLEURAL EFFUSIONS

BY THE REGULATION OF INTRATHORACIC PRESSURE DURING ASPIRATION (OXYGEN REPLACEMENT)

BY

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A NOTE UPON

THE COMPLETE REMOVAL OF PLEURAL EFFUSIONS

BY THE REGULATION OF INTRATHORACIC PRESSURE DURING ASPIRATION

(OXYGEN REPLACEMENT).[1]

ALTHOUGH paracentesis of the chest is such a common procedure it does not seem to be at all fully realised that the ordinary method of withdrawing the fluid by aspiration is most unsatisfactory. Aspiration in itself is not devoid of danger, and it is frequently the cause of considerable discomfort to the patient. It may be said, moreover, that as a general rule never more than 50 per cent. of the fluid present can be withdrawn at a single tapping ; and when, therefore, aspiration is used for the purpose of getting rid of an effusion, so as to allow of an examination of the lung by radioscopy and radiography, it is practically useless.[2] Symptoms of distress—e.g., cough and pain—often appear when only 1 or $1\frac{1}{2}$ litres of fluid have been withdrawn, yet the desire to take out as much fluid as possible does not infrequently tempt the operator to continue the aspiration after these symptoms have first appeared, thereby increasing the risks of œdema or of cardiac embarrassment When one side of the chest is full of fluid the removal of 1500 c.c. is regarded as most satisfactory, but skiagrams will show that there is still an astonishing amount of fluid left behind.

[1] The expenses of this investigation have been in part defrayed by a grant from the Graham Research Fund.
[2] There is no doubt that some of the discredit which has been so unjustly thrown on the value of skiagraphy in lung disease is due to this fact (compare Figs. 1 and 2).

Figs. 1 and 2 were taken before and after the withdrawal of
1000 c.c. In this case malignant disease of the lung was
suspected, and the effusion was tapped in the hope that the
lung would be sufficiently uncovered to permit of a diagnosis
being arrived at by the physical signs and skiagraphy. An
examination of these skiagrams shows, however, that the

FIG. 1.
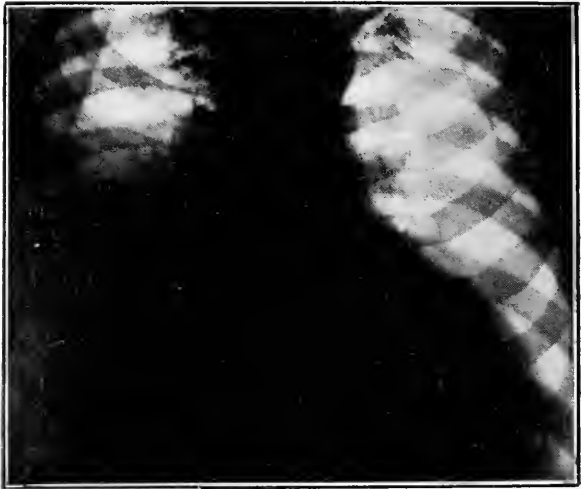
Right-sided pleural effusion in a man aged 75. There is dis-
placement of the heart and the mediastinum to the
left.

level of the fluid has been lowered barely one interspace by
the tapping, and that the root of the lung and the lower
lobes are still wholly obscured.

The reason of the apparent discrepancy between the
alteration in the level of the fluid in the second skiagram and
the withdrawal of over one litre of fluid is quite easy of

explanation. Before the tapping is done the pressure in the affected pleural cavity is either only slightly negative or even positive, the mediastinum and its contents are displaced to the opposite side, and the lung is collapsed. The effects of the removal of the fluid are to increase the negative pressure, to permit of the mediastinum and its contents to return to

FIG. 2.
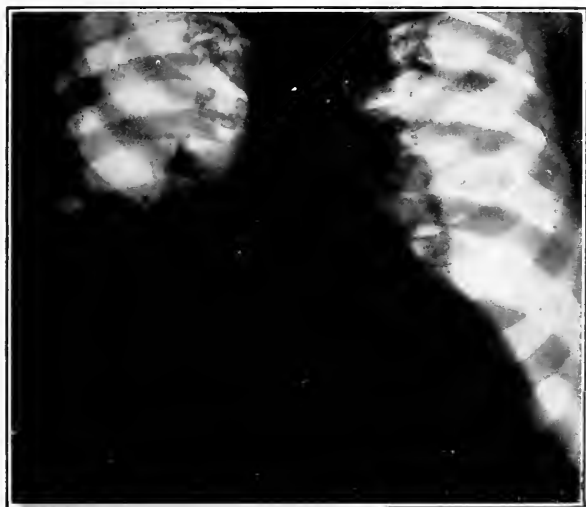
Skiagram of the same patient after 1000 c.c. of fluid had been drawn off. The level of the fluid has been lowered about one interspace only. The heart and mediastinum show much less displacement.

their normal position, and finally to allow the lung to expand ; it is only when this last change is taking place that the level of the fluid begins to sink.

As the chest is a closed chamber it is obvious that if fluid is withdrawn, either a rapidly increasing negative pressure

must be produced or the fluid must be replaced by some
other substance. In paracentesis both mechanisms are brought
into play, but there is a limit to the rapid alteration in the
position of the mediastinum and to the expansion of the
lungs when these are the seat of fibrotic changes or are
surrounded by a thickened or adherent pleura, and when the

FIG. 3.
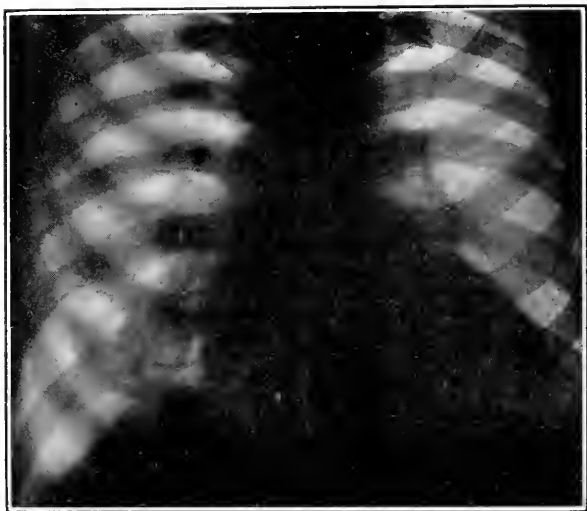
Skiagram of the same patient after the further removal of
1500 c.c. by the oxygen replacement method. The dia-
phragm is now visible, and the only fluid in the chest is a
small collection between the chest wall and the lateral
aspect of the diaphragm. Above this there is a small
pneumothorax. The whole of the lung is exposed, and a
shadow can be seen extending down from the hilum into
the lower lobe.

traction exerted on these by the increasing negative pressure
exceeds a certain grade the symptoms of distress so con-
stantly seen during paracentesis are produced.

The clear recognition of these facts suggests that if it were possible, during the process of withdrawing fluid, to modify the intrathoracic changes produced by the increasing negative pressure, by introducing from without some non-irritating sterile substitute, the whole of the fluid could be withdrawn. The most obvious substitute is air, but it is found that of the three principal gases of the atmosphere, oxygen when in contact with the pleura is absorbed rapidly, while the nitrogen and carbon dioxide are absorbed at a much slower rate. Since, however, it is desirable that the pneumothorax produced should be absorbed as quickly as possible I have used oxygen instead of air for the replacement of the fluid in all my cases.

Technique.—Fortunately, the methods which have been elaborated for the safe introduction into the pleura of measured quantities of nitrogen in cases of phthisis are equally applicable to the introduction of oxygen, and I have found Dr. Kornmann's apparatus, which I use for both nitrogen and oxygen pneumothorax, extremely convenient and easy of control. When, however, oxygen is being used as a substitute for fluid the needle designed for the introduction of nitrogen is useless, as the bore of the needle is very small and does not allow the transmission of the respiratory movements of the chest to the manometer, and it is, of course, an absolute *sine quâ non* that no gas is introduced into the chest unless the manometer, giving undulations which correspond with the respirations, indicates with certainty that the point of the needle is in the pleural cavity. I have, therefore, had made for me a needle and cannula which, as regards the shaft and its connexions, resemble in many ways an aspirating needle and cannula, but the lumen of the cannula is 1 mm. in diameter, and the point of the needle lies flush with the oblique and sharpened end of the cannula in the same manner as in a spinal needle and cannula.[3]

The patient lies in a semi-recumbent position well propped up in bed, turned slightly on to the sound side with the arm on the affected side well forward. The skin between the anterior and posterior axillary lines is painted with iodine, and the fifth and eighth intercostal spaces are marked in the

[3] This needle has been made for me by Messrs. Krohne and Sesemann.

mid-axillary line. A hypodermic needle filled with 2 per
cent. novocaine is first used, and an area of skin the size of
a threepenny-piece is infiltrated, and the needle of the
syringe is then pushed through the centre of this area into
the intercostal space. the piston being meanwhile driven
home. A small incision 3 mm. long is now made through
the infiltrated skin with a double-edged tenotome knife.
5 c.c. of novocaine are drawn up into a record syringe fitted
with a needle 5 cm. long ; the needle is passed through the
incision and pushed slowly through the intercostal space,
the novocaine being slowly injected all the time until the
point of the needle is felt to slip through the pleura. The
piston is then withdrawn and fluid should appear in the
syringe, giving evidence that the effusion has been reached
and confirming the nature of the same. When this has been
done in both interspaces the needle connected with the
aspirating bottle and vacuum pump is passed through the
lower anæsthetised area into the fluid. while the needle con-
nected with the oxygen apparatus is passed through the upper
anæsthetised area. It is hardly necessary to emphasise the
importance of testing both pieces of apparatus before use—
i.e.. seeing that fluid is sucked up through the one needle
into the aspirating bottle, and that oxygen does pass out
through the other needle. When the needles have been
introduced it is absolutely essential that the manometer
connected with the upper needle should show respiratory
movements, and until and unless these are obtained no
oxygen must be allowed to escape through the needle.
Fluid is now aspirated from the chest and the aspiration
continued until the patient either coughs or experiences the
slightest pain. The aspiration is then immediately stopped,
and 50 c.c. or 100 c.c. of oxygen are allowed to run in
slowly. The pain or cough will at once disappear, and the
aspiration is continued until the recurrence of some sym-
ptom demands the introduction of more oxygen. This
process is continued until no more fluid can be withdrawn.
Towards the end of the process oxygen will be found to
escape with the fluid, and the proportion of oxygen intro-
duced to fluid withdrawn must be increased.

If this procedure is carried out efficiently the patient
experiences practically no distress, either during or at the
end, and a skiagram taken at the conclusion will show the
almost complete disappearance of the fluid and a small
pneumothorax, while the lung, no longer obscured by the

fluid, permits of complete radioscopic and radiographic examination.

The following table shows the variations of the intra-thoracic pressure as recorded during such a procedure;

Amount of fluid withdrawn.	Symptom produced.	Intra-pleural pressure: inspiratory.	Amount of O_2 introduced.	Intra-pleural pressure: expiratory.†	Symptoms.
c.c.		mm. Hg.	c.c.	mm. Hg.	
685	Slight pain.	-8	100	-6	None.
285	Slight cough.	-16	100	-7	,,
$260 + O_2$	,,	-15	100	-10	,,
$200 + O_2$	Slight pain.	19	100	-13	,,
$170 + O_2$	,,	-26	100	-17	,,
$57 + O_2$	,,	-32*	100	-15	,,

* -22 mm. Hg expiratory.   † -2 mm. Hg at start.

while the skiagrams, Figs. 1 and 2, show the condition before paracentesis and after withdrawal of 1000 c.c. of fluid by the ordinary method, and Fig. 3, after the subsequent removal of a further 1500 c.c. by the oxygen replacement method. An interesting point will be noticed in the figures in the table relating to the intrapleural pressure. While at first pain is produced by a comparatively slight increase in the negative pressure, at each successive withdrawal of fluid a greater degree of negative pressure can be tolerated before any symptoms appear, until at the end the pressure during inspiration was -32 mm. Hg and during expiration -22 mm. Hg.[4]

I have so far endeavoured to show that by partially substituting oxygen for the fluid withdrawn the operation of paracentesis can be performed with a minimum of discomfort to the patient, and without the occurrence of those symptoms of distress so commonly manifested towards the conclusion, and often lasting for some time afterwards;

[4] I am indebted to Dr. Sydney Martin for allowing me to do an oxygen replacement aspiration in this patient and to publish the skiagrams.

that the whole, instead of only a portion, of the fluid can be withdrawn ; and that the lung can be cleared so as to permit of complete radioscopy and radiography. This method of oxygen replacement has still further advantages.

In certain cases, where there has been an inflammatory reaction of the pleura and the lung has been completely collapsed by fluid, the lung is incapable of any or of complete expansion owing to the thickening of the visceral pleura or to the formation of adhesions. When the lung is capable of partial expansion it is probable that if a steady traction could be exerted on its pleural aspect the adhesions and thickened pleura would gradually yield, and the visceral and parietal layers finally come into apposition. This can be effected if oxygen is allowed to replace the fluid. Two processes are at work in connexion with the intrapleural oxygen—the one an absorption of the gas and the other an interchange of gases. The absorption is the more rapid process, and in about 60 hours after the introduction of oxygen it will be found that most of the oxygen is absorbed, but there is still some gas in the pleural cavity ; this gas consists of nitrogen and carbon dioxide. These gases in their turn are absorbed, but more slowly. The effect of this is to produce a steady traction on the lung, which causes it slowly to expand. In some cases, it is true, there may be some reaccumulation of fluid, necessitating a second paracentesis with substitution of oxygen, but in all cases where the lung is capable of expansion the effect of the traction on the lung is marked.

The skiagram (Fig. 4) shows a lung in the process of expansion as the result of the removal of the fluid, with substitution of oxygen and the subsequent traction on the lung by the absorption of the gas.

When the lung is incapable of expansion it may be possible to relieve the patient of the weight and the discomfort of having one side of the chest filled with some 3 or 4 litres of fluid by replacing this fluid by oxygen. The value of the oxygen over nitrogen in such a case is that until the whole of the fluid has been drawn off it is impossible to estimate the degree to which the lung is bound down. If this fixation is complete oxygen is automatically replaced by nitrogen and carbon dioxide. Fig. 5 is a skiagram of a man who had a pyopneumothorax, the result possibly of the intrapleural rupture of a tubercular cavity. The pus was withdrawn by aspiration and oxygen intro-

FIG. 4.

Partial pneumothorax on the left side. When the patient was admitted the left pleural cavity was full of fluid, and the lung was in a state of complete collapse. The fluid was drawn off by oxygen replacement aspiration, and the skiagram shows the lung partially expanded as a result of the absorption of the oxygen. The previous attempts at emptying the pleural cavity by simple aspiration were unsuccessful, as the lung failed to expand and the fluid rapidly reaccumulated.

FIG. 5.
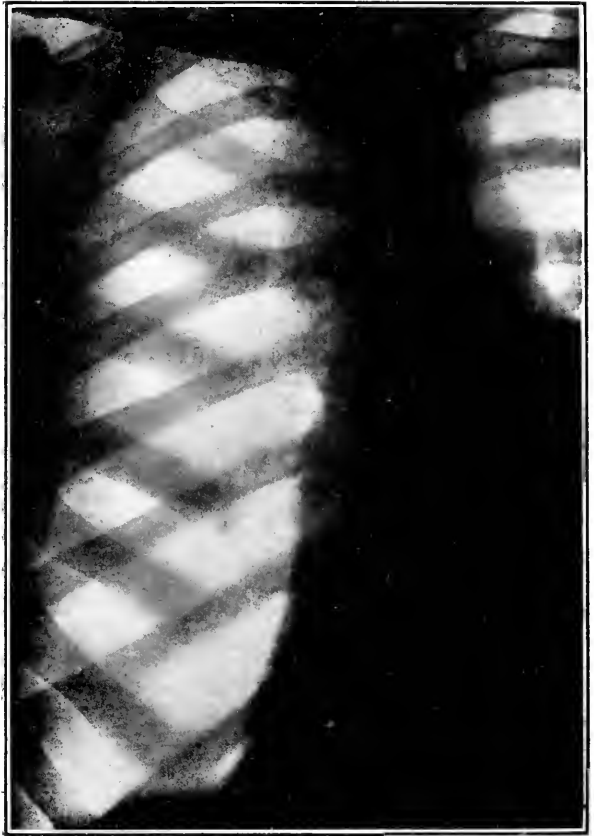
Complete pneumothorax. Lung collapsed and fixed by
adhesions. The patient had been admitted with a pyo-
pneumothorax; the pus was withdrawn by oxygen replace-
ment aspiration. This skiagram was taken a month later.

duced. The skiagram taken one month later shows no re-accumulation of fluid and only slight expansion of the lung. The patient had just returned after three weeks at a convalescent home. He had gained 8 lb. in weight, and stated that on the previous day he had walked for $4\frac{1}{2}$ hours.

The following analyses of the nature and interchange of gases within the pleural cavity of the patient just referred to were very kindly made for me by Sir William Ramsay :—

Analysis 1.—Of the gases in the pleural cavity at the time of admission: Nitrogen, 95·45 per cent.; CO, 4·55 per cent. No other gas present.

Analysis 2.—Of the gases in the pleural cavity after withdrawing 1250 c.c. of fluid and introducing 750 c.c. of oxygen: Nitrogen, 74·09 per cent.; oxygen, 21·56 per cent.; CO, 4·35 per cent.

Analysis 3.—Of the gases in the pleural cavity four days later: Nitrogen, 98·13 per cent.; oxygen, 0·69 per cent.; CO, 1·18 per cent.

Air has been used by various observers in the treatment of pleurisy and empyema, or to facilitate the withdrawal of fluid, and the first paper dealing with this subject was published by Parker in 1882 in THE LANCET. Since then papers have been published by Potain, Kawekara and Kawai, Forlanini, Barr, Holmgren, and others. The advantages of the accurate control of the intrathoracic pressure during aspiration and of the use of oxygen seem to be less fully appreciated.

[From the Bacteriological Laboratory. University College Hospital Medical School (Dr. F. H. Thiele).]

Some observations on the Wassermann's Reaction.

By F. H. Thiele and D. Embleton.

Introduction.

The following paper has been the result of a prolonged study of the Wassermann's reaction to endeavour to find out the true nature of the antibody reacting in it, and to correlate it to the various conditions producing somewhat similar results or giving rise to anticomplementary phenomena.

The nature of the various antigens has also been investigated to ascertain what the true antigenic substance really is and to determine its value in the presence or absence of various anticomplementary physical phenomena or substances. It has also been endeavoured to demonstrate how the presence of anticomplementary substances in the antigen or serum adjuvant one another and so tend to make the reaction hypersensitive.

Table I.

Amboceptor 1 in 10	100 cmm	90 cmm	80 cmm	70 cmm	60 cmm	50 cmm	40 cmm	30 cmm	20 cmm	10 cmm
Pure Complement 40 cmm	CH	CH	CH	CH	CH	CH	CH	CH	MH	MH / SH
„ 30 „	,,	,,	,,	,,	,,	,,	,,	,,	,,	,,
„ 20 „	,,	,,	,,	,,	,,	,,	,,	CH	,,	,,
1 in 10 „ 100 „	,,	,,	,,	,,	,,	,,	,,	MH	SH	,, / 0
1 „ 10 „ 90 „	,,	,,	,,	,,	,,	,,	MH	,,	,,	0
1 „ 10 „ 80 „	,,	,,	,,	,,	MH	MH	,,	SH	0	0
1 „ 10 „ 70 „	,,	,,	,,	,,	,,	,,	,,	,,	0	0
1 „ 10 „ 60 „	,,	,,	,,	,,	,,	,,	,,	,,	0	0
1 „ 10 „ 50 „	,,	,,	,,	MH	,,	SH	SH	0	0	0
1 „ 10 „ 40 „	,,	,,	,,	,,	SH	,,	0	0	0	0
1 „ 10 „ 30 „	MH	MH	MH	SH	,,	0	0	0	0	0

CH = Complete Haemolysis   SH = Slight Haemolysis
MH = Marked   „   0 = No   „

The heavy line shows the minimal quantity of Complement and Amboceptor necessary to cause complete haemolysis of 1 c. c. of a 1 % Red Cell suspension.

Adjuvant phenomena.

It was noted in our experiments that when two anticomplementary substances were mixed together their anticomplementary activity was greater in that mixture than the sum of the separate anticomplementary powers.

A. Anticomplementary power of Antigens.

In Wassermann's original method 0.1 c. c. of complement is taken as the standard and two units of amboceptor i. e., twice the amount which will with the above amount of complement cause complete haemolysis. Now from reference to Table I it will be seen that using 2 units of haemolytic amboceptor a much smaller amount of complement is necessary to cause complete lysis, thus an antigen can cause relatively and absolutely quite a large absorption of complement before any trace of inhibition of lysis becomes evident. The usual quantity used as unit of antigen is half that amount which just fails by this method to cause inhibition of lysis, and the unit of antigen will therefore contain quite an appreciable amount of masked anticomplementary substance. In Noguchi's method where accurate units of complement and amboceptor are used it is recommended that the anticomplementary action of an antigen should be studied in the presence of two units of each. Again referring to Table I it will be seen that by using 2 units of amboceptor (6 cmm), 9 cmms of complement are sufficient to cause complete haemolysis. Now for testing his antigen he uses 2 units of Complement, i. e., 40 cmms, hence before any anticomplementary action at all can be shown, 31 cmm of complement can be absorbed. There are thus really one and a half units of complement absorbed before any anticomplementary reaction becomes evident.

Noguchi (1) however recommends the use of only 4 times the quantity which will cause complete inhibition with a potent syphilitic serum. This places his „antigen unit" in a safe position as regards anticomplementary power, being well below the limits.

Browning and Mackenzie (2) determine their Minimal Haemolytic dose of immune body in the presence of 0.05 c. c. of Complement, and the Minimal haemolytic Complement dose in the presence of 4—5 doses of Immune body. Reference to Table I will not help us here since the observers have exceeded the limits of the table. On referring to their book we find that the M. H. D. of Complement was most commonly 5 cmm.

Now they admit that their lecithin cholesterin antigen absorbs 1—3 doses and, as will be seen by reference to their paper in some experiments apparently nearly up to 6 doses of complement. i. e., from 5—15 to 30 cmm, showing that their antigen is anticomplementary $\frac{1}{4}$—$\frac{3}{4}$, to nearly $1\frac{1}{2}$ units of complement according to the system of Table I.

We have obtained specimens of their antigen and find it anticomplementary to even a greater amount than stated above.

Thus it becomes apparent that the units of antigen adopted in the various methods are appreciably anticomplementary.

B. Summation and adjuvant action of two anticomplementary substances.

Sera very frequently contain anticomplementary substances usually exceedingly small in amount when first drawn but becoming greater on standing, as is frequently the case in sera tested for the Wassermann's reaction. The anticomplementary property may be thermolabile or thermostable. The former is usually due to bacterial activity in the serum subsequent to withdrawal.

We thought that the mixture of an anticomplementary antigen with a slightly anticomplementary serum might possibly give a fallacious slight positive reaction. It was found, as can be seen from the adjoined table, that an anticomplementary serum in the presence of an anticomplementary antigen causes the absorption of more complement than the sum of complement absorbed by the two components separately.

Table II.

Complement { Units and { quantity	1 20 cmm	1½ 30 cmm	2 40 cmm	2½ 50 cmm	3 60 cmm	3½ 70 cmm	4 80 cmm	5 100 cmm	6 120 cmm
Horse serum 100 cmm	MI	SI	VSI	0	0	0	0	0	0
(A) Antigen 600 cmm (anticomplementary)	,,	,,	0	0	0	0	0	0	0
Horse serum 100 cmm } (A) Antigen 600 cmm }	CI	CI	CI	CI	CI	CI	CI	MI	MI
(B) Antigen 600 cmm (not anticomplementary)	0	0	0	0	0	0	0	0	0
Horse serum 100 cmm } (B) Antigen 600 cmm }	MI	SI	VSI	0	0	0	0	0	0

CI = Complete Inhibition   SI = Slight Inhibition
MI = Marked   ,,   VSI = Very slight Inhibition

The anticomplementary serum above tested showed slight inhibition with 2 units of Complement, hence less than one unit of Complement was free, so that rather more than one unit must have been absorbed.

In the case of the antigen; when 1½ units of complement were used there was only incomplete haemolysis, there-

fore one unit was not free, therefore rather more than half a unit was absorbed. The sum of the two together make up just more than $1\frac{1}{2}$ units: or again. if $2\frac{1}{2}$ units of Complement are added to the horse serum 1 unit is free because there is complete haemolysis, so that at the outside $1\frac{1}{2}$ units are absorbed. In the case of the antigen when 2 units of complement were added complete haemolysis occurred showing that at least one unit was free and that at the outside one unit was absorbed; so that the sum total of absorption for the two is $2\frac{1}{2}$ units at the outside.

From the experiment however we found that the two together caused the complete absorption of at least four units.

The reason for quoting an experiment with horse serum was that there could be no possibility of any fallacy due to the unexpected presence of syphilitic antibody. The same experiment has been repeated several times with absolutely normal human sera which have become anticomplementary on standing and similar results obtained.

Thus it will be seen that experimenters are liable to error who use,

1. Anticomplementary antigens.

2. Very "sensitive" systems.

Complement Inhibitory power of Sera.

A. Reaction of Corpse sera with "syphilitic" antigens.

Historical.

The Wassermann's reaction with the sera of corpses has been the object of a great deal of observation in the last few years. The first observers Fränkel (3), Much (4), Pick (5). Proskauer (6), believed that it was as accurate in these as when the serum was obtained during life, and so a large number of conditions found at the autopsy were regarded as syphilitic.

Subsequent observers however began to doubt the accuracy of the results. It was noted that besides really specific cases not giving a positive result with this reaction, others which were undoubtedly non specific did, the majority of the latter were cases of Tuberculosis. Pneumonia. Carcinoma and terminal infections. Some observers got as much as 25 % of non specific cases giving a positive Wassermann's reaction with the sera obtained post mortem. Lubarsch (7) out of 100 positive sera had 41 which were from non syphilitic cases, forming 7.3 % of all sera examined by him for the purpose.

From our observations it would appear that many of the so-called positive Wassermann's reactions with corpse sera are really due to the above mentioned adjuvant phenomenon.

Nearly all corpse sera are anticomplementary. This property is partly thermolabile and thermostable, the relative amounts vary, the thermostable is usually the predominant.

Most corpse sera have a thermostable anticomplementary power varying from a quarter to two units or more of Complement in 100 cmm. It is rare to find a serum which is not anticomplementary to at least a quarter of a unit in 50 cmm.

This is for sera which are quite free from a tinge of haemoglobin.

Table III.

Complement { units / quantity }		1 / 20 cmm	1¼ / 25 cmm	1½ / 30 cmm	1¾ / 35 cmm	2 / 40 cmm	2¼ / 45 cmm	2½ / 50 cmm	2¾ / 55 cmm	3 / 60 cmm	
Serum of Corpse Inactive											
1. Cardiac	100 cmm	MI	MI	SI	0	0	0	0	0	0	4 hrs. after death
2. Pneumonia	100 „	CI	CI	CI	CI	CI	MI	SI	0	0	24 hrs. „ „
3. Carcinoma	100 „	SI	SI	0	0	0	0	0	0	0	10 hrs. „ „
4. Meningitis	100 „	„	0	0	0	0	0	0	0	0	16 hrs. „ „
5. Mitral disease	100 „	CI	CI	CI	CI	CI	MI	MI	SI	SI	10 hrs. a. d. clear and light colour.
6. Gastric ulcer haemorrhage	100 „	SI	SI	SI	SI	0	0	0	0	0	8 hrs. after death
7. Septicaemia	100 „	MI	„	„	0	0	0	0	0	0	6 hrs. „ „
8. Carcinoma	100 „	„	„	0	0	0	0	0	0	0	5 hrs. „ „
9. Osteomyelitis	100 „	SI	0	0	0	0	0	0	0	0	10 hrs. „ „
10. Cardiac	100 „	CI	CI	CI	CI	CI	CI	CI	CI	CI	24 hrs. „ „ dark colour
Serum of Corpse Fresh											
1. Fresh	100 cmm	CI	MI	MI	SI	SI	0	0	0	0	
2. „	100 „	„	CI	CI	CI	CI	CI	CI	MI	SI	
3. „	100 „	MI	SI	SI	0	0	0	0	0	0	
4. „	100 „	„	„	0	0	0	0	0	0	0	
5. „	100 „	CI	CI	CI	CI	CI	MI	MI	SI	SI	
6. „	100 „	SI	SI	SI	0	0	0	0	0	0	
7. „	100 „	MI	MI	MI	SI	SI	0	0	0	0	
8. „	100 „	SI	SI	SI	„	0	0	0	0	0	
9. „	100 „	„	0	0	0	0	0	0	0	0	
10. „	100 „	CI	CI	CI	CI	CI	CI	CI	CI	CI	
Cerebro Spinal Fluid Inactive											
1. Cardiac	200 cmm	CI	CI	CI	CI	CI	MI	MI	SI	SI	8 hrs. after death blood present
2. Pneumonia	200 „	„	„	„	„	„	CI	„	„	„	idem
3. Septicaemia	200 „	„	„	„	„	„	„	„	MI	„	6 hrs. after death no blood
4. „	200 „	„	„	„	„	„	CI	„		MI	
5. Carcinoma	200 „	0	0	0	0	0	0	0	0	0	Perfectly clear 6 hrs. after death

The above table is taken from 10 consecutive observations from a large number of cases.

With regard to the cerebro spinal fluid, there was usually no anticomplementary reaction if the fluid was drawn free from blood, the slightest tinge of blood ad-mixture gave a marked anticomplementary reaction.

The fluid from some septic cases gave a marked anticomplementary reaction even though the fluid was quite free from blood.

Many of the corpse sera were even more anticomplementary than those mentioned above.

For the purpose of demonstrating the adjuvant phenomenon it is only necessary to have an antigen and serum each anticomplementary to the extent of a quarter of a unit, to together cause absorption of from three quarters to one and a half units of Complement. Which quantity would be sufficient to give an apparently positive Wassermann's reaction.

The following experiments as set forth in the adjoining table IV were made to demonstrate the adjuvant phenomenon with a mixture of anticomplementary substances of minimal anticomplementary power. The nine anticomplementary substances were graded so that the quantity used was anticomplementary to less than a quarter of a unit of Complement, i. e., 5 cmm, so that the sum of the anticomplementary power of any two was less than half a unit, i. e., 10 cmm of Complement.

When however the combinations of the two were made it was found, as can be seen by reference to the table, that the anticomplementary power instead of being equal to less than half a unit was equal to $3/4 - 1 1/2$ units, i. e., instead of the anticomplementary power being equal to less than 10 ccm of Complement it was equal to from 15 to 30 cmm.

This occurred also when the individual substances were used in double quantities.

Table IV.

Mixtures of anticomplementary substances of minimal anticomplementary power.

Complement { Units / Quantity emm	1 / 20	1¼ / 25	1½ / 30	1¾ / 35	2 / 40	2¼ / 45	2½ / 50	2¾ / 55	3 / 60	Calculated Anti-compl. Power	Proved Anticompl. Power
1. A. Serum normal on standing	100 emm	VSI	OI	OI	OI	OI	OI	OI	OI	OI	—	less than ¼ unit
2. B. id.	60 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
3. C. ,,	80 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
4. D. ,,	50 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
5. E. Serum Corpse	40 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
6. F. ,, ,,	60 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
7. G. Serum Horse on standing	30 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
8. Cholest. susp.	200 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
9. Lecith. non antig.	300 ,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	—	,, ¼ ,,
10. A. Serum	200 ,,	MI	MI	SI	SI	,,	,,	,,	,,	,,	less than ½ unit	,, 1 ,,
11. B. ,,	120 ,,	,,	,,	,,	OI	,,	,,	,,	,,	,,	id.	,, ¾ ,,
12. C. ,,	160 ,,	,,	,,	,,	SI	SI	,,	,,	,,	,,	,,	1¼ ,,
13. D. ,,	100 ,,	,,	,,	,,	,,	OI	,,	,,	,,	,,	,,	1 ,,
14. E. ,,	80 ,,	,,	,,	MI	MI	SI	SI	,,	,,	,,	,,	1½ ,,
15. F. ,,	120 ,,	,,	,,	SI	SI	OI	OI	,,	,,	,,	,,	1 ,,
16. G. ,,	60 ,,	,,	,,	,,	,,	SI	,,	,,	,,	,,	,,	1¼ ,,
17. Cholesterin as (8)	400 ,,	,,	,,	,,	,,	OI	,,	,,	,,	,,	,,	1 ,,
18. Lecithin as (9)	600 ,,	,,	,,	,,	,,	SI	,,	,,	,,	,,	,,	1¼ ,,
19. A. Serum 100 ,, } Cholesterin 200 ,, }		,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	1¼ ,,
20. B. Serum 60 ,, } Cholesterin 200 ,, }		,,	,,	,,	,,	OI	,,	,,	,,	,,	,,	1 ,,
21. C. Serum 80 ,, } Cholesterin 200 ,, }		,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	1 ,,
22. D. Serum 50 ,, } Cholesterin 200 ,, }		,,	,,	MI	,,	SI	,,	,,	,,	,,	,,	1¼ ,,
23. E. Serum 40 ,, } Cholesterin 200 ,, }		,,	,,	,,	,,	,,	SI	,,	,,	,,	,,	1½ ,,
24. F. Serum 60 ,, } Cholesterin 200 ,, }		,,	,,	,,	,,	,,	OI	,,	,,	,,	,,	1¼ ,,
25. G. Serum 30 ,, } Cholesterin 200 ,, }		,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	1¼ ,,
26. A. Serum 100 ,, } Lecithin 300 ,, }		,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	1¼ ,,
27. B. Serum 60 ,, } Lecithin 300 ,, }		,,	,,	SI	OI	OI	,,	,,	,,	,,	,,	¾ ,,
28. C. Serum 80 ,, } Lecithin 300 ,, }		,,	,,	MI	SI	SI	SI	,,	,,	,,	,,	1½ ,,
29. D. Serum 50 ,, } Lecithin 300 ,, }		,,	,,	SI	,,	,,	OI	,,	,,	,,	,,	1¼ ,,
30. E. Serum 40 ,, } Lecithin 300 ,, }		,,	,,	,,	,,	,,	,,	,,	,,	,,	,,	1¼ ,,

Complement {	Units Quantity cmm	1 20	1¼ 25	1½ 30	1¾ 35	2 40	2¼ 45	2½ 50	2¾ 55	3 60	Calculated Anti-compl. Power	Proved Anticompl. Power
31. F. Serum Lecithin	60 cmm } 300 ,, }	MI	MI	SI	SI	SI	OI	OI	OI	OI	less than ¼ unit	1¼ unit.
32. G. Serum Lecithin	30 ,, } 300 ,, }	,,	,,	,,	,,	..	SI	..	,,	,,	id.	1½ ,,
33. A. Serum B. ,,	100 ,, } 60 ,, }	,,	,,	,,	,,	OI	OI	,,	..	..	..	1 ,,
34. C. ,, D. ,,	80 ,, } 50 ,, }	,,	,,	,,	,,	SI	SI	,,	..	..	..	1½ ,,
35. E. ,, F. ,,	40 ,, } 60 ,, }	,,	SI	,,	,,	,,	..	..	..	..	..	1½ ,,
36. B. ,, C. ,,	60 ,, } 80 ,, }	,,	,,	,,	,,	OI	OI	,,	..	..	..	1 ,,
37. D. ,, E. ,,	50 ,, } 40 ,, }	,,	MI	,,	..	SI	,,	..	,,	..	..	1¼ ,,
38. F. ,, A. ,,	60 ,, } 100 ,, }	,,	,,	..	,,	,,	..	..	..	,,	..	1¼ ,,

If however a non-anticomplementary antigenetic substance is used alone with an anticomplementary serum there will be no difference between the control and antigen containing tubes, and the anticomplementary inhibition of haemolysis is evident.

Occasionally, however, it was found that with an anti-complementary antigen a corpse serum would cause the absorption of more complement than would be expected by the adjuvant phenomena alone. In these cases it was found that complement was also absorbed when a non anticomplementary antigen was used, e. g., the Noguchi antigen.

This must be regarded as a true Complement fixation in the Wassermann sense. It, however, has been noted in cases where there was absolutely no possibility of Syphilis.

The question then arises as to

(1) why this fixation occurs,

(2) what the anticomplementary power of the serum is due to,

(3) the relationship between the fixation and anticomplementary power.

In the corpse sera giving the above mentioned fixation there must be a substance similar to that in Syphilitic serum

which is capable of combining with the active lipoid in the Antigen and thus causing the absorption of more complement. Should this combination have already occurred the serum would absorb complement without the presence of "antigen" and thus we conclude that an anticomplementary serum is one in which the above mentioned combination may have taken place but in which the complement absorption affinity has not become saturated. Against this point at first slight would be the fact of the presence of free complement in these anti-complementary corpse sera. To explain this we quote the following observation:

> If with 30 cmm of corpse serum no haemolysis occurs in a haemolytic system with 2 units of Complement, but with $2^1/_4$ units slight haemolysis occurs; the serum is then not completely anticomplementary to $2^1/_4$ units, so that if now one unit more Complement were added complete haemolysis would be expected to occur, this is however found not to be so — it being necessary to add at least $1^1/_4$—$1^1/_2$ units of Complement and sometimes considerably more.

From this one would deduce that an anticomplementary substance acts on the principle of the greater the amount of Complement present the greater the absorption. Thus appearing to conform with the laws of mass action and adsorption.

In this way we can account for the presence of free complement in an anticomplementary serum, and a serum absorbing more complement even when there is free complement already present. Further, complement titration shows that very little or no complement is present in many corpse sera.

The next question arises as to the absence of an anticomplementary reaction in clear cerebro-spinal fluids. From the chemical point of view on examination these give no evidence of any increase in albuminous or lipoid constituents as compared with normal, and they only show an anticomplementary reaction where they have become tinged with blood serum or where there has been inflammatory change in the meninges, or intense septic processes in the body.

If the anticomplementary power of a corpse serum is due to the combination in the body of an "antigen" and "antibody", then if the antibody can be shown to be in excess in some

cases, one might expect the "antigen" to be in excess in others. The latter has been occasionally demonstrated as is seen by the following observations.

Table V.

	Complement		1	1¼	1½	1¾	2	2¼	2½	2¾	3	units
A. Corpse Serum	100 cmm		MI	MI	SI	—	—	—	—	—		
A. Corpse Serum Syphilitic Serum	100 100	„ } „ }	CI	CI	MI	MI	SI	—	—	—		
B. Corpse Serum	100	„	„	„	CI	CI	CI	MI	MI	SI	SI	
B. Corpse Serum Syphilitic Serum	100 100	„ } „ }	„	„	„	„	„	CI	CI	MI	MI	
Syphilitic Serum	100	„	—	—	—	—	—	—	—	—	—	

Thus in some anticomplementary sera we can demonstrate

1. Excess of "antigen",
2. Excess of "antibody", and
3. Account for the presence of unabsorbed complement

and we can deduce that in some anticomplementary sera two substances have united like "antigen" and "antibody" and that the complement affinity has not become saturated.

On this observation can be explained the occasional disappearance in Syphilitic corpse sera of the Wassermann's reaction which was positive before death.

We shall now discuss as to how the anticomplementary substances are formed in the body.

It has been shown by some observers that if tissue e. g., kidney or liver is incubated with chloroform in serum that the serum develops substances which give a positive Wassermann's reaction.

We have taken guinea-pigs, killed them, washed them out with normal saline, and incubated pieces of the liver and kidneys in sterile normal saline at 37° C. for varying periods and have shown that the filtered fluid gives a marked anticomplementary reaction, but we have never been able to obtain a convincing true Wassermann reaction.

We never obtained the reaction under 24 hours incubation. The fluids were tested to see that they were perfectly bacteriologically sterile. The anticomplementary substance is thermo-stable and can be developed equally well from liver kidney or heart.

In the following table, the quantities of tissue used were in the proportion of 1 gramme to 10 c. cs. of normal saline.

Table VI.

		Quantity of fluid cmm	With 1¼ units Compl. gave	With 5 units of Antigen and 1¼ Compl. gave		Quantity of fluid cmm	With 1¼ units Compl. gave	With 5 units of Antigen and 1¼ units of Compl.
Kidney	24 hrs.	20	OI	OI	48 hrs.	20	MI	MI
,,	id.	40	,,	,,	id.	40	,, CI	,, CI '
,,	,,	60	,,	,,	,,	60	CI	CI '
,,	,,	80	,,	,,	,,	80	,,	,,
,,	,,	100	SI	SI	,,	100	,,	,,
Liver	24 hrs.	20	OI	OI	48 hrs.	20	MI	MI
,,	id.	40	SI	SI	id.	40	CI	CI
,,	,.	60	MI	MI	,,	60	,,	,,
,,	,,	80	,, CI	,, CI	,,	80	,,	,,
,.	,,	100	CI	CI	,,	100	,,	,,

5 Units of·Antigen alone were not anticomplementary to 1¼ units of complement.

From our previous observations re the adjuvant action of anti-complementary substances, the above if mixed with an anticomplementary antigen would cause marked absorption of complement in excess of the control tubes and so account for the Wassermann's reaction noted by other observers.

It would thus appear that when a tissue undergoes aseptic autolysis it developes an anticomplementary property. Now during the process of autolytic degradation of tissues the lipoidal substances are dissociated from their protein combinations and undergo changes resulting in their splitting up and forming new combinations, also there is a small increase in cholesterin. The protein substances also start on a process of degradation. The amount of cholesterin newly formed is very small indeed and its amount is quite insufficient to account for the reaction.

The substance in the syphilitic serum etc. which appears capable of acting as an "antibody" is one which is closely associated with the euglobulin fraction, since it has been shown that in Syphilitic cerebro spinal fluids and urines the positive reaction runs in the majority of cases parallel to the euglobulin content.

Then again Zinsser and Johnson (8) have shown that the thermolabile anticomplementary property is closely related to the globulin fraction.

Noguchi in dealing with thermostable anticomplementary substances extracted the blood with ether, then evaporated the ethereal solution, treated this residue with hot benzol. The soluble part was dried and extracted with cold acetone. The insoluble fraction of this contained lecithins etc. The soluble portion, cholesterins, fatty acids, neutral fats etc. The former was not anticomplementary, the latter was. This was undoubtedly solely due to the cholesterin present.

We have made a series of experiments which show that the anticomplementary power of thermostable anticomple-

mentary sera is contained in the globulin fraction, or something precipitated in combination with it, and that the "antigen-antibody" combination produced when a syphilitic serum is incubated with a suitable antigen is also precipitated in a similar way and will directly absorb complement and is thermostable.

Thus clear anticomplementary corpse sera were taken, mixed with an equal volume of a saturated ammonium sulphate solution and well shaken. After precipitation had occurred the whole was thoroughly centrifuged — the supernatant fluid removed and the precipitate repeatedly washed with half saturated ammonium sulphate solution, the precipitate was then taken up in normal saline to make up to the original bulk.

It was then found that this saline solution of the precipitated material was almost if not quite as anticomplementary as the original serum.

Similar results were obtained with a markedly anticomplementary uraemic serum.

In the case of Syphilitic sera — the serum was taken and an active antigen was added so that the two were in combining units, the mixtures were incubated for 1—2 hours. At the end of that time the serum was treated as above with saturated ammonium sulphate solution. The precipitate was similarly treated, and made up to the original bulk of the serum and it was found that the solution absorbed added complement. There was no cholesterin or any other known anticomplementary substance present.

The solution of the precipitate was thermostable.

Table VII.

Original		Complement			
		25 cmm	30 cmm	40 cmm	50 cmm
Corpse serum 1.	100 cmm	CI	CI	CI	MI
„ „ 2.	100 „	„	„	MI	SI
Uraemic serum	100 „	„	„	CI	MI
Normal serum	100 „	0	0	0	0
Suspension of precipitate					
Corpse serum 1.	100 cmm	CI	CI	MI	SI
„ „ 2.	100 „	„	„	SI	SI
Uraemic serum	100 „	„	„	CI	MI
Normal serum	100 „	0	0	0	0

Original	Complement			
	25 cmm	30 cmm	40 cmm	50 cmm
Syphilitic serum with the necessary antigen 100 cmm precipitate brought up to original bulk of serum 100 cmm	CI ..	CI „	CI MI	CI MI
Normal serum with the same amount of antigen	0	0	0	0

From these results it would appear that there is a great similarity between the anticomplementary substance in the anticomplementary sera and the combination of syphilitic antigen and antibody, in their relation to the globulin fraction, behaviour towards complement and thermostability.

B. Complement inhibitory power of other sera.

Various observers have stated that the blood of patients in the uraemic state and those suffering from acute infective processes gives a positive Wassermann's reaction. Likewise the sera from patients who have had prolonged anaesthesia with ether, chloroform, etc.

The evidence here again is that these sera are all anticomplementary, the anticomplementary power is thermostable and adjuvant phenomena as described above can be observed.

Our own observations show that the anticomplementary power is also present in the fresh unheated serum in the above mentioned conditions. Occasionally the anticomplementary power becomes increased after heating. This may be due to

(a) the inactivation of free complement present in the serum which previously to some degree masked the full anti-complementary power;

(b) to altered physical chemical conditions produced by heating or standing. This will explain the occurence of anti-complementary properties in normal animal sera which have been heated to various degrees, e. g., rabbit, dog. The following table shows a series of some of the conditions investigated.

Table VIII.

Sera Inactiv. 30 min. at 55°C		1 20	1¼ 25	1½ 30	1¾ 35	2 40	2¼ 45	2½ 50	2¾ 55	3 9? cmm	Complement units Guinea pig serum
Ether Serum	100 cmm	CI	CI	CI	CI	CI	MI	SI	—		Intrav.*) 24 hrs. previously
„ „	100 „	„	„	„	„	MI	SI	—			Intravenous 3 days previously
„ . „	100 „	„	„	„	„	CI	CI	MI	SI		„ 25 hrs. „
„ „	100 „	„	„	„	„	„	MI	„	„	— —	open ether „ „ „
„ „	100 „	„	„	„	„	„	MI	„	SI	— —	„ „ 24 „ „
„ „	100 „	„	„	„	„	CI	„	„		— —	„ „ „ „
Chloroform Serum	100 „	„	„	„	„	MI	SI	—	—	—	„ „ „ „
„ „	100 „	„	„	„	„	CI	MI	MI	SI	— —	„ „ „ „
„ „	100 „	„	„	„	„	MI	„	SI	„		„ „ 22 „ „
„ „	100 „	„	„	„	„	CI	CI	MI	MI	SI —	„ „ 17 „ „
Bromide	„ 100 „	„	„	„	„	„	„	„	SI	— —	
„ „	100 „	„	„	„	„	„	MI	SI	„	— —	
Sulphonal	„ 100 „	„	„	„	„	„	CI	CI	MI	SI —	Case of Poisoning
Uraemia	„ 100 „	„	„	„	„	„	„	MI	SI	— —	*)
„	„ 100 „	„	„	„	„	„	„	„	SI	— —	
„	„ 100 „	„	„	„	„	„	MI	SI	„	— —	
„	„ 100 „	„	„	„	„	MI	SI	„		— —	
Trypanosome	„ 100 „	„	„	„	„	CI	CI	CI	CI	CI CI	Guinea pig Nagana
Septicaemia	100 „	„	„	„	MI	MI	SI	SI	—	— —	Streptococcal
Tuberculosis	„ 100 „	„	„	„	„	„	„	„	—	— —	Miliary
„	„ 100 „	„	„	CI	„	„	„		— —		
Typhoid	„ 100 „	„	„	„	„	MI	SI	SI	—	—	Severe Toxaemia 2nd. week

*) These two sera showed further absorption of complement to the extent of ½ unit = 10 cmms in the presence of a non anticomplementary antigen.

The ether serum case was again investigated after 10 days and was found to give a completely negative Wassermann's reaction.

The uraemic case showed no evidence of Syphilis at the autopsy.

Here again, we have present in the serum of these cases a substance which will combine with a non anticomplementary antigen, and cause further absorption of complement as if there were still unsaturated „antibody" present to combine with the active lipoid antigen.

Also the adjuvant phenomenon occuring if these sera are mixed with anticomplementary antigen will give the apparent positive Wassermann reactions that have been noted. So that with an imperfectly controlled system the following sera might give erroneous positive Wassermann's reactions.

1. From a corpse.
2. From patients suffering from acute infections.
3. From patients after anaesthesia etc.
4. From patients suffering from uraemia.

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Possible factors interfering with a haemolytic amboceptor complement system.

1. Complementoids have a greatly diminished affinity for the amboceptor, and in the presence of complement are prevented from combining, although occasionally when antigen, amboceptor and complementoid are incubated together complementoid will combine and prevent the union of active complement subsequently added.

Now the conditions under which the Wassermann experiments are conducted never allow of complementoid being present alone, without the complement. So that the anticomplementary action cannot be due to this.

2. Anticomplements. The only possible ones which could produce anticomplementary phenomena in the conditions under investigation would be auto-anticomplements. These, in the sense as originally described by Ehrlich have no bearing on the present phenomena.

3. The question of poisoning the complement will be discussed in a later section.

4. When a specific precipitate occurs complement becomes bound and is no longer capable of activating a rabbit haemolytic system. In these observations the sera used are human and guinea-pig, now no specific precipitin for the one occurs in the other. Thus the anticomplementary power of a human serum when mixed with guinea-pig's complement is not due to this cause.

5. Alteration in the physico-chemical conditions in sera. The reason why some sera become anticomplementary when heated to a certain degree would appear to be due to the fact that the temperatures to which the sera have to be heated to make them anticomplementary are such that a beginning coagulation precipitation of the albuminous matter occurs just like the formation of a very fine precipitate due to a specific precipitin and in this condition it is well known that complement absorption can take place.

So that this may explain some of the anticomplementary power of heated rabbit's and dog's sera. Dog's sera have to be heated to 60° C to make them anticomplementary. At 56° C

they are not so, hence the complement cannot mask the anti-complementary power if it were present from the beginning.

6. Action of Cholesterin.

Cholesterin undoubtedly exerts an anticomplementary effect as has been repeatedly shown.

The anticomplementary power varies with different specimens. We have observed that half a milligramme is sufficient to cause complete inhibition of $1\frac{1}{4}$ units of Complement (25 cmm). Now it is questionable if in any condition cholesterin is present in the serum in such amount that 0.1 c. c. of the serum contains half a milligramme of cholesterin. Many of the sera in this amount are anticomplementary to 60 cmm of Complement so that if the anticomplementary power were due to this, the amount present would have to be very large. In most of the anticomplementary antigens cholesterin is by far the most potent and most abundant anticomplementary factor.

The anticomplementary power of some ether and corpse sera where there is haemolysis may possibly be to some extent accounted for by the presence of liberated cholesterin.

We have also observed that cholesterin in addition to acting as an anticomplementary substance in some way affects red cells which have been in contact with it, so that more amboceptor-complement is required to haemolyse them, after they have been centrifuged and washed free from the cholesterin, than when not previously treated with cholesterin.

7. Interference by non specific proteids and their degradation products.

Noguchi (1) has shown that non-specific proteids or their cleavage products may in the presence of normal fresh sera cause the absorption of complement and so prevent the occurence of haemolysis.

This however cannot be considered to be the cause of the thermostable anticomplementary phenomenon mentioned, since Noguchi showed that the phenomenon occurred with non inactivated sera only.

However, it may account for non specific fixation with fresh sera added to "syphilitic" antigens containing proteids and their degradation products, e. g. alcoholic extracts of fresh

but more especially of autolysed organs, such as syphilitic foetus livers, which are frequently more or less autolysed.

8. The possibility of a ready-made "antigen-antibody" combination in some of the above mentioned sera.

We have shown in the case of clear sera from corpses that such a substance may be assumed to be present as is evidenced by occasional variations whereby the serum may:

(1) in the presence of a non anticomplementary lipoidal antigen combine with more complement, like in a true Syphilitic Wassermann's reaction;

(2) in the presence of a Syphilitic Serum combine as "antigen" and fix more complement;

(3) the antigen-antibody combination of a Wassermann's reaction is thermostable like the anticomplementary power of the serum;

(4) that the anticomplementary substance is closely related to the globulin fraction of the serum like the specific antibody antigen combination;

We have also shown that some "Ether" and uraemia sera fix more complement when mixed with a non anticomplementary antigen (see table VII).

Then again, the anticomplementary power of an autolysed sterile tissue would appear to be best explained on the above assumption. It would not appear to be due to cholesterin:

(1) because very little increase occurs in cholesterin during autolysis;

(2) that alcoholic extraction of normal organ dissolves out much more cholesterin and it is much less anticomplementary than the saline extract of the autolysed organ.

In uraemia there is distinct evidence of a greatly increased tissue katabolism as can be deduced from the great increase in non-coagulable nitrogen in the serum.

In acute infections the thermostable anticomplementary power is accompanied by greatly increased tissue breaking up.

We can then summarise that anticomplementary substances appear in the serum where there is increased organ destruction, such as occurs during and after death; from the influence of protoplasmic poisons such as sulphonal, narcotics

and anaesthetics; in uraemia and acute infections. They also appear in sera where bacterial processes have occurred causing degradation changes.

In all these processes proteids and their cleavage products are set free and phosphatids are liberated from their existing combinations, undergo various changes and can thus enter upon new combinations of the nature of non specific "antigen" and "antibody".

Production of Antibody giving Complement fixation with lipoidal and other antigens used for Wassermann's reaction.

In a paper by Dr. Batty Shaw (9) and one of us it was shown that by repeatedly inoculating a rabbit with carefully washed out rabbit's kidneys, heart, brain and liver, the rabbit's serum became capable of fixing complement in the presence of antigen, made by extracting dried finely powdered guinea-pig's kidneys with normal saline. The kidneys, heart and brain were most potent, the liver much less so.

We now find that, by injecting rabbits in the same way, complement fixation phenomena occur with not only extracts of fresh organs, but with lipoids obtained by alcoholic extraction, crude or after precipitation by acetone.

We also found that injecting rabbits with heterogenous organs did not give rise to the same phenomena.

We also took rabbit's own blood collected in sodium citrate and inoculated it into the peritoneal cavity, but noted no complement fixing properties in the serum subsequently. Through the kindness of Mr. Barrington we had the opportunity of examining a castrated rabbit which had been inoculated with its own testicular substance and found that its serum gave a slight but obvious Wassermann reaction.

Thus we were able to obtain antibodies in the serum of these rabbits, giving complement fixation, like in the Wassermann's reaction, with lipoidal antigens by the inoculation of:

1. Homogenous tissues.
2. Autogenous tissues.
3. But not by Heterogenous tissues.

Bruck (10) was unable to produce "antibodies" of a similar nature by injecting human liver into rabbits, but only got them by inoculating Syphilitic foetus livers. This may have been due to the spirochaetes since rabbits inoculated with spirochaetes give a Wassermann reaction.

More lately Di Cristina, M. Cipolla (11) has produced syphilitic "antibodies" in rabbits by inoculating the nucleo albumins from a syphilitic foetus liver.

The question here again arises as to the part played by the spirochaetes.

We also found that removal of the lipoids from the homogenous tissues did not interfere with the production of the antibodies.

Table IX.

	Quantity of inactive serum	Complement units					Antigen
		1	1½	2	2½	3	
1. Rabbit after 8 injections of Rabbit Kidney	cmm 100	CI	CI	CI	CI	MI	Alcoholic guinea-pigs heart
2. Rabbit after 8 injections of Rabbit Brain	100	„	„	CI	MI	SI	id.
3. Rabbit after 8 injections of Rabbit Liver	100	„	MI	SI	—	—	„
4. Rabbit after 2 injections of Rabbit Kidney	100	„	CI	MI	SI	—	„
5. Rabbit after 2 injections of its own Testicles	100	„	MI	VSI	—	—	„
6. Rabbit after 5 injections of its own Blood	100	SI	SI	—	—	—	„
7. Rabbit after 5 injections of Cat's Kidney	100	„	—	—	—	—	„
8. Rabbit after 5 injections of Cat's Liver	100	„	—	—	—	—	„
9. Serum of a normal Rabbit	100	„	—	—	—	—	„
10. „ from No. 1	100	CI	CI	CI	MI	SI	Non-anticomplementary Noguchi antigen
11. „ „ „ 2	100	„	CI	CI	MI	SI	id.
12. „ „ „ 3	100	MI	MI	SI	—	—	„
13. „ „ „ 4	100	„	MI	MI	SI	—	„
14. „ „ „ 5	100	„	SI	—	—	- -	„
15. „ „ „ 6	100	SI	—	—	—	—	„
16. „ „ „ 7	100	—	—	—	—	—	„
17. „ „ „ 8	100	—	—	—	—	—	„
18. „ „ „ 9	100	—	—	—	—	—	„
19. Serum from rabbit inoculated with lipoid free rabbit's kidney	100	CI	CI	CI	MI	Sl	„
20. Serum from rabbit inoculated with lipoid free rabbit's liver	100	MI	MI	SI	—	—	„

With regard to the differences between the effects produced by iso- and autogenous tissues on the one hand and heterogenous tissues on the other, it would appear that the constituents of the latter rapidly disappear from the blood getting anchored on to suitable tissue receptors subsequently giving rise to the specific precipitins etc., whereas with the former there are no receptors on to which the constituents

absorbed from the inoculated tissues could anchor and so they remain circulating in the blood for a long time. The lipoidal parts probably being fairly quickly got rid of as they can be used up by the tissues of the inoculated animal; there being no specificity of fats.

Metchnikoff showed that Tetanus Toxin could be demonstrated for 4 months after inoculation into a tortoise whose cells have no receptors for the toxin.

Again antibodies produced in one animal can be shown to remain much longer in the blood of another animal inoculated with them, if the animal be of the same species than if it be of another.

We have noticed the serum of rabbits inoculated with iso-tissues retain the complement fixation reaction with lipoids for about 4 months.

We would therefore conclude that the "antibody" in the serum of these rabbits is due to the presence of degradation products of the iso-tissues inoculated.

As far as we have been able to see, the sera of the inoculated rabbits did not develop precipitins, etc., for rabbits' organ cells and proteids, thus showing that no specific iso-antibody was produced, again proving that the inoculated proteids did not become fixed to tissue receptors.

We did not obtain any evidence of the complement fixing substance when the rabbit's own blood was inoculated. With the testicular substance however more was produced, but small in amount. Testicular substance has been shown by several observers to be like heterogonous tissue.

Nature of the Syphilitic Antibody.

We conceive that in syphilis a similar slow tissue degradation takes place, and that these degradation bodies in the presence of lipoidal antigens cause complement fixation. In the majority of cases of secondary syphilis this body is present in large quantity, the greater part free and ready to combine with lipoidal antigen when exposed to it and so cause absorption of complement, and a varying proportion already combined in the circulation with active lipoids thus accounting for the increased anticomplementary power of the majority of

syphilitic sera. Now in cases of malignant syphilis it is found that there is little or no complement fixing antibody whereas the anticomplementary power is relatively high. This can be explained on the assumption that the greater part of the "antibody" has gone into combination with the free lipoids in the circulation and so very little fixation with a further amount of lipoids is possible.

Peritz (12) showed that a positive reaction could be made to disappear by injecting into the patient a large quantity of lecithin. His observations were confirmed by Marelli (13). Thus showing that the reaction can take place in vivo.

What however has not been demonstrated by these observers is that the serum became more anticomplementary. Unfortunately we have not had an opportunity of injecting lecithin into a patient who gave a positive Wassermann's reaction. Bruck and Stern (14) were unable to confirm the above observation.

Further support of this view is given by our observations on anticomplementary sera:

(1) That anticomplementary sera may still combine with more non anticomplementary lipoidal substances and absorb still more complement.

(2) That such sera may also act as antigens with syphilitic sera.

Thus demonstrating the excess of either "antigen" or "antibody".

In these anticomplementary sera the degradation occurs at such a rate that the lipoid has not had time to be completely got rid of and so there is sufficient of the lipoid present to combine with the "antibody" and so in the majority of cases a true Wassermann is not obtained.

This would occur in uraemia, death, and acute infections.

Where the breaking up is slower, e. g., in Syphilis, Leprosy etc., the combination either does not occur because the degradation is much slower (it takes at least 48 hours autolytic degradation before marked anticomplementary phenomena are noted in tissues incubated at $37\,^{\circ}$ C), and the lipoids as they are set free become katabolised.

The other possibility is that in slower degradations the lipoidal combination is being continuously excreted and so is

only present in the serum in small quantity giving a slight anticomplementary reaction, and that the uncombined antibody gives the fixation on subsequent treatment with a lipoidal antigen. It has been observed by one of us (15) that degradation products of proteid go into combination with lipoids and become water soluble and easily excretable.

(3) That there is a great similarity between the reacting substance in anticomplementary sera and the combination of syphilitic antibody and antigen, as has already been demonstrated. Thus we would account for the difference being due solely to varying rates of tissue change and degradation.

Antigenic properties of antigens.

The "Antigenic" properties of the various antigens recommended appear to depend, according to the mode of extraction and the material used, upon fixation due to the presence of:

1. Active Lipoidal Substances.
2. Extracts of Spirochaetes.
3. Anticomplementary phenomena arising from:
    a) Anticomplementary substances e. g. Cholesterin.
    b) The physical state of the Antigenic Emulsion.
    c) Albuminous substances (non-specific fixation. N o - g u c h i).

With regard to the spirochaete content which might make the extract of syphilitic foetus liver act as a true antigen for a true B o r d e t - G e n g o u phenomenon:

1. There is no parallelism between the antigenic value of an extract and the number of spirochaetes present.

B o a s (16), S c h l i m p e r t (17) and our own observations.

2. If this were a true antigen, the reaction with this extract should still be obtained when the „non" specific lipoid reaction has disappeared, when the patient is cured as it does in all other infections. e. g.. Typhoid. No observer has yet demonstrated this. We ourselves have also been unable to obtain this with numerous extracts, many of which were obtained from organs extremely rich in spirochaetes.

3. Again as the patient gets better the complement fixation gets less in the case of W a s s e r m a n n 's reaction with lipoids or syphilitic organ extracts, whereas with a true antigen the reverse should be the case. Thus we should conclude that the antigenic value of a watery extract depends not on the number spirochaetes or any specific substance connected with syphilis, but on some substance which acts as an "antigen".

The observations of Polack Daniels (18) are of interest in connection with this. This observer has noted that after complete saturation of a syphilitic serum with guinea pig heart antigen, there still remained in the syphilitic serum some amboceptors which became bound on the addition of an extract of syphilitic foetus organ and vice-versa.

From this he deduces that there are two sets of antibodies present, one "non specific" which will bind with any lipoids and a true specific syphilitic antibody which is not bound by these but becomes bound with the extract of spirochaetes in the syphilitic organ antigen. One weak point is this, if the syphilitic serum be first exposed to the syphilitic antigen the whole of the antibodies should be removed, viz., the true ones for the spirochaetes, and the non specific lipoidal fixable ones, and none should be left for fixation on subsequent exposure to the guinea-pig heart antigen, which however was not found to be the case by Polack Daniels (18).

Now the experiments of Polack Daniels were repeated in the following way:

Only using Guinea-pig antigen, or human heart antigen.

Complement used was 0.1 c. c.
Haemolytic Amboceptor. Twice the amount necessary to cause complete lysis with 0.1 c. c. complement.
Antigen. Guinea-pig's heart or human heart 1 in 10 absolute alcohol.
Unit used: half the amount which was just slightly inhibitory by itself.
Syphilitic serum 0.04 c. c.

Table X.

Tubes	1	2	3	4	5	6	7	8	9
1st. hour	G. C. S.	G. C. S.	G. C. S.	G. C. S.	G. C. S.	G. C. S.	G. C. S.	G. C. S.	G. C. S.
2nd.	Hb.	G.	G. C.	G. C.	G. C.	G. C.	G. C.	G. C.	G. C.
3rd.	—	Hb.	Hb.	G.	„	„	„	„	„
4th.	—	—	—	Hb.	Hb.	G.	„	„	„
5th.	—	—	—	—	—	Hb.	Hb.	G.	„
6th.	—	—	—	—	—	—	—	Hb.	Hb.
Result	CI	CI	VMI	CI	OI	MI	OI	SI	OI
Doses Antigen	1	2	2	3	3	4	4	5	5
„ Compl.	1	1	2	2	3	3	4	4	5

H. = Human heart antigen; G. = Guinea pig antigen; S. = Syphilitic serum; C. = Complement; Hb. = Haemolytic system (Red cells, haemolytic amboceptor added separately).

Table XI.

Tubes	1	2	3	4	5	6	7	8	9	10	11
1st. hour 2nd. 3rd.	H.C.S. Hb.	H.C.S. H. Hb.	H.C.S. H.C. Hb.	H.C.S. H.C. H. Hb.	H.C.S. H.C. Hb.	H.C.S. H.C. H. Hb.	H.C.S. H.C. Hb.	H.C.S. H.C. H. Hb.	H.C.S. H.C. Hb.	H.C.S. H.C. H. Hb.	H.C.S. H.C. Hb.
4th. 5th. 6th. 7th.	— — — —	— — —	— — —	— —	— —	— —	— —	—	—		
Result	CI	CI	MI	CI	OI	CI	OI	MI	OI	ZI	OI
Doses Antigen	1	2	2	3	3	4	4	5	5	6	6
„ Complement	1	1	2	2	3	3	4	4	5	5	6

Using Guinea-pig and human heart antigen together.

Tubes	1	2	3	4	5	6	7	8	9	10	11
1st. hour 2nd. 3rd.	G.C.S. Hb.	G.C.S. H. Hb.	G.C.S. G.C. Hb.	G.C.S. G.C. H. Hb.	G.C.S. G.C. Hb.	G.C.S. G.C. H. Hb.	G.C.S. G.C. Hb.	G.C.S. G.C. H. Hb.	G.C.S. G.C. Hb.	G.C.S. G.C. H. Hb.	G.C.S. G.C. Hb.
4th. 5th. 6th. 7th.											
Result	CI	CI	MI	CI	OI	CI	OI	VMI	OI	VI	OI
Doses Antigen	1 G.	1 G., 1 H.	2 G.	2 G., 1 H.	3 G.	3 G., 1 H.	4 G.	4 G., 1 H.	5 G.	5 G., 1 H.	6 G.
„ Complement	1	2	2	3	3	3	4	4	5	5	6

From these results it will be seen that without using syphilitic organ extract similar results may be obtained to those of Polack Daniels. It would appear to be therefore a phenomenon of summation and adjuvant actions of anti-complementary substances and also of mass action and concentration, and is not due to the specific rôle of the extract of the spirochaetes and the true syphilitic antibodies.

The addition of an extra quantity of Guinea-pig heart antigen caused a further degree of inhibition as did the addition of human heart antigen. It is just possible that the human heart antigen may bind the amboceptors better than the guinea-pig heart antigen, but there is definitely no need for spirochaete extracts to explain the phenomena observed by Daniels.

With regard to the other factors various observers have drawn attention to the following:

1. That an ethereal solution of a phosphatid when shaken up in normal saline does not make a good antigen, whereas an alcoholic solution of the same, shaken up in normal saline does.

2. That this is not due to different phosphatids being present in the different extracts, but only due to differences in the physical condition of the same substances.

Thus, if an alcoholic extract is evaporated and taken up in ether its "antigenic" properties are said to be very much less than if the emulsion is made from the alcoholic solution direct: on the other hand, the addition of a little alcohol or acetone to the saline suspension of a primary ethereal extract greatly increases the turbidity and the "antigenic' value.

Thus Munk (19) says that if a good Guinea-pig heart alcoholic antigen is evaporated and taken up in ether, the extract becomes useless as an antigen when shaken up in normal saline, and if a Guinea-pig heart is extracted with ether, the suspension of this is useless as an antigen unless acetone or alcohol are added.

From these observations it would appear that the antigenic value does not depend on the chemical constitution of the phosphatids extracted but on their physical conditions at the time of being brought into contact with the syphilitic serum. Thus ether dissolves from the tissues the "cuorin" like fraction and the mono-amido-phosphatid lecithin. Alcohol leaves the cuorin behind but dissolves the free mono-amido lecithin and the bound phosphatid.

Then again it is said commercial ovo-lecithin in ethereal solution is useless as an antigen whereas in alcoholic solution it is potent.

Now looking at the varieties of phosphatids in the various solutions we have:

Primary Ether Extract	Alcoholic Extraction of Primary Ether Extract	Primary Alcohol Extract	2nd. Ether of Primary Alcohol
Cuorin Lecithin	— Lecithin	Lecithin diamido (?) phosphatid	Lecithin diamido (?) phosphatid

Thus there is no difference in the phosphatids in the primary alcoholic extract and the secondary ether extract of this — so that the difference, according to these observations in the behaviour of the two solutions must be wholly due to their physical conditions.

The secondary alcoholic extract of the primary ethereal extract differs in the absence of cuorin; now cuorin is not anti-antigenic, as is seen by the fact that the addition of alcohol to the ethereal extract direct increases the "antigenic" value even in the presence of the cuorin — in fact one of the factors in the causation of the increase in complement absorption power in this case may be due to the precipitation of the small amounts of cuorin by the alcohol, cuorin being alcohol insoluble.

From our own observation on the purified lipoids, we conclude that the chemical constitution as far as has been at present established, bears no relation to the antigenic value of a lipoid.

Sachs and Rondoni (20) have shown that the more turbid the emulsion in greater the "antigenic" value. Thus if an alcoholic solution of a phosphatid is added drop by drop to normal saline the result is a very much more turbid and antigenic emulsion than if the alcoholic extract is added in bulk. Now with ether solutions added to normal saline there is very little turbidity and the "antigenic" power is low, but it becomes increased on the addition of alcohol.

The turbidity only means that the lipoid has become thrown out in colloid form from its alcoholic solutions by the addition of normal saline. This forms the so called suspension colloid, and as a result the surface tension becomes greatly increased. So that we can deduce that the more turbid the emulsion the greater surface tension and the more "antigenic" it should be.

On the other hand lipoids in ethereal solution cannot be made to pass into the colloidal state.

The lipoids here appear to be present in the Solform closely related to the hydrophil colloids, if they are not even really true solutions in ether, in distinction to the alcoholic solutions.

From these observations it would appear that with the non-specific lipoid "antigens" used in the Wassermann's reaction the whole "anti-

genic" value turns upon the physical conditions and that the known chemical constitution is a matter of little or no importance.

This would appear to be confirmed by the fact that emulsions of vaseline and shellac which form good colloidal suspensions act as "good antigens". All observers however do not quite agree — several have shown that extracts made in the same way and producing emulsions of like turbidity do not have equal antigenic power.

We have found:

1. That pure phosphatid solutions in ether do act as good antigens in saline suspension.

2. That a pure phosphatid solution in ether which does not act as a good antigen does not have this property conferred upon it by adding alcohol to its saline suspension.

3. That a pure phosphatid in ethereal solution which was a "good antigen" and had subsequently lost its antigenic power did not have the latter restored on the addition of alcohol to the emulsion in saline, or by being dissolved in alcohol and then emulsified.

4. That pure phosphatids, preserved dry, also lost their antigenic value and that this was not restored on making an alcoholic solution and suspending in normal saline.

5. That the antigenic value of a given sample of antigen bears no relation to the amount or kind of phosphatid present.

6. That an antigen which in ethereal suspension in normal saline had marked antigenic power, on being made into a colloidal suspension from alcohol in normal saline in addition acquired marked anticomplementary properties. These latter being parallel to the degree of turbidity produced.

From these observations we would conclude:

1. That there are phosphatids or substances brought down with phosphatids which act as potent antigens even when the phosphatids are not in the colloidal state.

2. That a phosphatid which has no antigenic value does not have this conferred upon it by being made to pass into the colloidal state — all that happens is that it becomes anticomplementary.

3. That when a phosphatid passes into the colloidal state it becomes anticomplementary, but does not have its true antigenic properties if present taken from it.

So that when a syphilitic serum is added to an antigen of this description we get complement absorption from:

a) The anticomplementary physical state of the antigen.

b) The union of "antigen" proper and antibody.

c) From any anticomplementary power that may be present in the serum itself which is usually unobserved by the methods commonly employed.

Now taking into consideration the adjuvant phenomenon previously dealt with, it will be seen that the complement absorption will be greater than the sum of the absorptions due to the three factors separately.

Also the complement absorption will be much greater than can be accounted for by factors a, c. and the adjuvant phenomenon, thus showing that the antigen has true "antigenic" properties.

4. If on the other hand a phosphatid is a "poor antigen" then we get the complement absorption from the same factors as above but the amount absorbed by the true combination of antigen and antibody is so small that it would not give a positive reaction except for the occurence of the adjuvant phenomenon.

Finally we would conclude that an antigen owes its antigenic properties to some substance which has the same solubilities as, or is closely bound to the phosphatids, not to its physical state and not to the amount or known constitution of phosphatid present. We have repeatedly noted that a potent antigen, usually the acetone insoluble phosphatid variety, suddenly loses its antigenic power, and this is accompanied by the formation of a precipitate in the previously clear antigen solution. If an antigen is tested during the process of this change, it is seen to have developed marked anticomplementary properties.

Thus we had an acetone insoluble phosphatid antigen, which reacted as follows in ethereal suspension in normal saline (0,3 grammes of the lipoid were dissolved in 10 ccm of ether; of this a 1 in 10 suspension in normal saline was made).

It was:

1. Non haemolytic in 500 cmm.

2. Non-anticomplementary in 500 cmm to a $\frac{1}{4}$ unit (5 cmm) of Complement.

3. Antigenic in 2 cmm, using 5 units of syphilitic serum and 2 units (40 cmm) Complement. With this there was complete inhibition.

On week after this test had been made it was noticed that a precipitate was forming. Now the results were:

1. Non haemolytic in 500 cmm.

2. Non anticomplementary in 80 cmm. but anticomplementary in 90 cmm to $1/4$ unit of Complement (5 cmm).

3. Antigenic as before.

A week later the clear supernatant solution was taken and tested, the results being:

1. Non haemolytic as above.

2. Non anticomplementary in 200 cmm but in 220 to $1/4$ unit, 5 cmm of Complement.

3. Antigenic value — nil.

The precipitate was suspended in saline and tested, and was found tobe non antigenic and did not impart antigenic powers on addition to the clear supernatant solution or to a non antigenic phosphatid, but was somewhat anticomplementary.

It was insoluble in water, ether, alcohol and acetone, and the amount was insufficient for further examination. We propose to deal with this in a later paper.

It is therefore probable that the real antigenic power is due to a combination of this precipitated substance with the phosphatid and when the combination is broken up either during or after extraction the antigenic power is destroyed.

The criterion of a real "antigenic" antigen is the presence of this combination and not the physical state of the lipoid this is simply adjuvant.

Rôle of Anticomplementary bodies in the Wassermann's reaction.

It has been shown that the majority of antigens used in the Wassermann's reaction are anticomplementary either from:

a) the presence of anticomplementary substances in crude extracts,

b) the physical state of the antigen at the time of the reaction,

c) the addition of an anticomplementary substance like cholesterin.

It has already been shown that cholesterin is not antigenic in itself. We have previously demonstrated that cholesterin cannot endow a "non antigenic" antigen with antigenic properties, and cannot assist in the

extraction of an antigenic substance from an organ. It remains now merely to discuss the statement of Browning and Mackenzie (2), Sachs (21) and others, that though cholesterin alone has no antigenic effect, mixtures of cholesterin and lecithin give a particularly specific reaction with syphilitic serum. These authors lay it down that if the addition of cholesterin is capable of increasing the quantity of complement absorbed beyond the amount absorbed by lecithin alone this is an indication of the syphilitic nature of the serum. They go on to state that if the amount thus absorbed is in excess to the amount of 5 of their units (= 25 cmm of Complement) the diagnosis is absolute.

Now by referring to our Table IV, it will be seen that even by combining substances of minimal anticomplementary power the sum of the two being less than 2 of the above units i. e., 10 cmm, the absorption is found to be 25 cmm i. e., 5 of their units.

In the Wassermann's reaction the anticomplementary effect produced by the union of an antigen and antibody is by far greater than the anticomplementary power of any of these sera. Now if we refer to Table II we see that the antigen used is anticomplementary to the extent of about 10 cmm i. e. 2 of the above units (which is the average amount of anticomplementary power possessed by the cholesterin lecithin antigen alone, in the quantities used) the horse serum by itself was anticomplementary to about 20 cmm of Complement. i. e. 4 of the above units (which would be the quantity of complement absorbed by the union of a syphilitic antigen and weak antibody) by mixing the two, instead of getting the expected complement absorption of about 30 cmm i. e. 6 of their units, we get absorption of 80 cmm i. e. 16 of their units. Thus we see that the addition of a small amount of anticomplementary substance, itself only equivalent to two of their units, may cause an increased absorption of 10 of their units i. e. 50 cmm.

From this we should expect that the addition of an anti-complementary substance e. g., cholesterin, in such amount that it is anticomplementary to the extent of 10 cmm i. e. 2 of the above units, to a lecithin antigen which was capable of absorbing with the syphilitic serum 20 cmm i. e. 4 units, should give the absorption of 10 of these units in excess of the sum of the two.

	Complement	
	Quantity	B. and M. units
Thus we have a lecithin antigen which in the presence of syphilitic serum is capable of absorbing	20 cmm	i. e. 4 units
Adding cholesterin anticomplementary to . .	10 ,,	,, 2 ,,
We should expect the sum of the two to be .	30 ,,	,, 6 ,,
We however get absorbed	80 ,,	,, 16 ,,
So that there is absorbed in excess	50 ,,	,, 10 ,,

So that with a w e a k syphilitic serum the addition of cholesterin to the antigen causes the absorption of 10 units of complement in excess of that absorbed by the serum and antigen alone. In the case of a s t r o n g syphilitic serum the adjuvant phenomenon is even more marked rising by geometric progression rather than by arithmetic.

This phenomenon is not characteristic of a syphilitic serum reacting with cholesterin, but is simply characteristic of any complementary serum whether so from the beginning or after reaction with an antigen.

Thus will be seen from the following table.

Table XI.

	4	6	8	10	12	14	16	20	24
B. and M. units	4	6	8	10	12	14	16	20	24
Complement units	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$	3	$3\frac{1}{2}$	4	5	6
Quantity cmm	20	30	40	50	60	70	80	100	120
1. Lecithin Antigen + Syphilitic Serum	MI	SI	VSI	—	—	—	—	—	—
2. Lecithin Antigen (from 1) + Cholest.	,,	,,	—	—	—	—	—	—	—
3. Lecithin Antigen (from 1) + Cholest. + Syphilitic Serum	CI	CI	CI	CI	CI	CI	CI	MI	MI
4. Normal Anticomplementary Serum	MI	SI	VSI	—	—	—	—	—	—
5. Normal Serum (from 4) + Lecithin and Cholesterin (from 2)	CI	CI	CI	CI	CI	CI	CI	MI	MI
6. Normal Serum (from 4) + Noguchi Antigen	MI	SI	VSI	—	—	—	—	—	—

Now the adjuvant phenomenon also will have the following tendency — viz., where the lecithin is not antigenic, to cause a considerable absorption of complement in the tube to which the cholesterin has been added in addition, in the presence of an anticomplementary serum.

As the majority of syphilitic sera are anticomplementary the difference in absorption between the two experiments will be considerable.

When the antigen however is weakly "antigenic" a very weak syphilitic serum will cause with the lecithin a very slight unrecognisable absorption of complement, but this becomes magnified and therefore observable in the experiment where the anticomplementary cholesterin is present in addition. The obvious danger of this system is that it will give differences in the amount of complement absorption between the lecithin and lecithin cholesterin mixtures due to anticomplementary phenomena alone.

It is due to this phenomenon that many observers still uphold the original Wassermann's reaction. For the same reason turbid emulsions are "good antigens", e. g. vaseline etc.

Fate of the Complement.

The complement in this reaction may become fixed or rendered useless possibly in the following ways.

1. In that it becomes completely combined in the antigen antibody combination just as it does when antigen combines with its specific amboceptor.
2. It may be mechanically absorbed when a precipitation or agglutination occurs.
3. It may be destroyed by fermentation action (Manwaring, 22) or poisoned (Kiss etc., 23).

Now dealing with the latter Michaelis and Skwirsky (24) first showed that in the Wassermann's reaction the whole of the complement did not become bound or destroyed. That after the reaction had taken place the end piece of the complement was undamaged and uncombined so that it could cause the haemolysis of persensitised red cells. This disposes of the ideas of Manwaring and Kiss etc.

Now further work has shown that no conclusion can be drawn with regard to the nature of the antibodies taking part in a reaction by the determination of the presence or absence of unabsorbed end piece of the complement. The absorption of the two pieces is simply a matter of time (Gengou, 25).

Noguchi (26) has shown from observations with an anti-human goat's haemolytic serum that complement which has been absorbed in the following reactions,

1. Meningo-coccus — anti-meningo-coccus serum.
2. human — anti-human serum.
3. egg — anti-egg serum.
4. Wassermann's reaction.

though unable to activate rabbits' haemolytic serum was able to activate the goats' haemolytic serum, thus the goats' amboceptor had apparently a

more potent complementophilic receptor and was able to attract complement which had been absorbed in the above reaction.

We obtained from Dr. Bolton an anti-human haemolytic goats' serum of a titre of 10 cmm on our system, and tested with

(1) antigen and antibody of the third order: Cholera, anticholeraic lytic serum.
(2) antigen and receptor of the second order: Typhoid and typhoagglutinating serum, egg and anti-egg.
(3) In the Wassermann's reaction.
(4) In complement absorption by an anticomplementary serum or substance: Cholesterin.

We found that with

(1) Antigen and receptor of the third order, that the complement was completely fixed and no activation of the human goat haemolytic system occurred, no haemolysis occurring even in 48 hours at room temperature after the usual incubation period.

(2) With receptors of the second order, the complement could activate the anti-human haemolytic goat system, but not the anti-human haemolytic rabbit system though in the case of the goat serum the haemolysis was usually delayed — taking place more rapidly, the smaller the number of binding units of the antigen and second order receptors.

(3) The same applied to the Wassermann's reaction as in the above series (2).

(4) In the case of anticomplementary sera, the haemolysis was always very rapid, and the sera tested never gave complete inhibition with the rabbit system and two units of complement.

The possibilities when the goat's haemolytic amboceptor becomes activated by the guinea-pig's complement in 2. 3. 4 are.

A. That the complement of the guinea pig is of two kinds
(a) fixable
(b) non fixable
in the reaction, but that the non fixable is capable of activating the goats' haemolytic amboceptor.

B. That the complement can be pulled out by reason of its greater affinity for the goats' amboceptor.

That the latter is more probably the case is seen from 1. above where with receptor of the third order no free non-fixable complement is present.

Therefore in 2. 3. 4. the complement absorption is of a similar nature and in the Wassermann's reaction may be due to beginning precipitation and anticomplementary phenomena.

Zusammenfassung.

1) Die komplementbindende Eigenschaft eines Antigens ist unabhängig von dem Reichtum an Spirochäten, deren Produkten oder Veränderungen, verursacht durch ihre Anwesenheit.

2) Es ist kein Grund vorhanden zu glauben, daß syphilitische Organextrakte Antikörper binden, die nicht durch nichtsyphilitische Extrakte gebunden werden.

3) Ein nichtspezifisches Antigen verdankt seine antigene Eigenschaft einer Substanz, die nur in ganz kleinen Mengen vorhanden ist, und die eng an die Phosphatide gebunden ist.

4) Ein Antigen verdankt seine Eigenschaften nicht dem physikalischen Zustand des Antigens zur Zeit der Verwendung, auch nicht wohlbekannten antikomplementären Substanzen. z. B. Cholesterin.

5) Die antikomplementäre Eigenschaft eines Antigens beeinflußt und erhöht wesentlich die hemmende Eigenschaft eines Serums, die entweder präexistieren oder nur nach Behandlung mit einem Antigen zustande kommen. Hierdurch können gelegentlich falsche Schlüsse gezogen werden.

6) Der syphilitische Antikörper, der in dieser Reaktion die Rolle spielt, ist nicht ein Antikörper im strengen Sinne genommen und ist nicht nur für Syphilis, Lepra etc. charakteristisch, sondern ist vermutlich nur ein Stadium in der Entstehung einer antikomplementären Kombination, die zustande kommt, wo Gewebe ziemlich rasch verfallen, sowie bei akuten Infektionen, Autolyse, Narkose, Tod etc.

Bei Syphilis etc. ist der Prozeß langsamer und die Kombination wird erst durch Behandlung mit einem aktiven Lipoid vollzogen.

7) Die Seren von urämischen Patienten oder von denen, die einer Narkose unterworfen waren, auch in akuten Infektionen und Leichensera besitzen antikomplementäre Eigenschaften und geben gewöhnlich keine echte Wassermannsche Reaktion.

Es ist uns gelungen, in manchen von diesen Seren die Anwesenheit eines Ueberschusses an Antigen oder Antikörper zu demonstrieren, wodurch wir den obengenannten Parallelismus beweisen konnten.

8) Der antikomplementäre Komplex wird mit der Globulinfraktion gefällt gleich dem syphilitischen Antikörper, einerlei ob er in freiem Zustande oder an das Antigen gebunden ist.

9) Das Komplement in der Wassermannschen Reaktion wird gebunden gleichwie bei Rezeptoren II. Ordnung und kann wieder frei gemacht werden.

Das Komplement wird nicht vergiftet oder durch Fermente vernichtet.

10) Wenn man zwei antikomplementäre Substanzen zusammenmischt, so wird die komplementadsorbierende Kraft des Gemenges viel größer als die Summe der Mengen, die durch die einzelne Komponente der Mischung allein adsorbiert wird.

In dieser Weise verursacht die Beimengung einer antikomplementären Substanz, wie Cholesterin, zum Antigen in der Wassermannschen Reaktion eine erhöhte Komplementadsorption, die viel größer ist als die Summe der Quantitäten, die gebunden werden durch die Reaktion und durch das antikomplementäre Vermögen des Cholesterins. Auf diese Weise wird die Reaktion wesentlich empfindlicher gemacht, indem sehr viel Komplement adsorbiert wird. Dies ist aber in keiner Weise eine Eigenschaft, die dem syphilitischen Serum allein zukommt, sondern es geschieht immer, wenn zwei antikomplementäre Substanzen zusammengemischt werden.

Dies Vermögen nennen wir das Adjuvant Phaenomenon.

11) Durch die Injektion von Geweben homogener Herkunft erwirbt das Serum das Vermögen, eine echte Wassermannsche Reaktion zu geben.

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Active and passive Hypersensitiveness to Tubercle bacilli and the relation to the Tuberculin reaction in man.

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With 1 Curve.

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Historical.

A large amount of literature has already appeared bearing on this subject, but the results in most cases have been negative and inconclusive. Numerous observers, Friedemann (1), Eitner and Storch (2), Röpke und Busch (3), Onaka (4), Novotny (5), Simon (6), Fränkel (7), Kraus (8) etc. have failed to produce passive sensitisation in guinea-pigs with the blood or serum of tuberculous individuals who reacted to tuberculin.

Bauer (9) reported passive hypersensitiveness to tuberculin in guinea-pigs by inoculating them with the blood of tuberculous patients. He relied on febrile reactions when these animals were inoculated with tuberculin but other observers drew attention to the occurrence of febrile reaction in guinea-pigs which had been previously inoculated with normal human serum [Novotny (5), Fränkel (7), Simon (6)].

Yamanouchi (10) injected the serum of tuberculous patients intraperitoneally into young rabbits and subsequently inoculated tuberculin intravenously. The animals died acutely. Krause (11) however drew attention to the extreme sensitiveness of young rabbits to the intravenous inoculation of tuberculin. Further the symptoms noted by Yamanouchi cannot be regarded as characteristic of anaphylaxis.

Bruck (12) inoculated subcutaneously into guinea-pigs 5 c.c. of the serum of patients who reacted vigorously with old tuberculin. After 48 hours he inoculated 0.5 c.c. of old Tuberculin subcutaneously. The guinea-pigs, ten in all, developed the symptoms of anaphylaxis and died within one hour. Post mortem examination showed no particular characteristic change. Bruck does not give his "anaphylactic" symptoms.

Dealing next with the inoculation of tissues of tuberculous patients and animals.

Bail (13) experimented by inoculating guinea-pigs with the tissues of tuberculous animals. He stated that they could be sensitised in this way. His experiments are not convincing since none of the typical symptoms of anaphylaxis were produced. He further stated that with blood and serum he was unsuccessful. Friedberger (16) produced active anaphy-

laxis in guinea pigs after sensitisation with Tubercle bacilli, and passive hypersensitiveness by inoculating antituberculin (Höchst).

Onaka (4) repeated these experiments and stated that he got positive results with the tissue inoculations. Kraus, Löwenstein and Volk (8) were unable to confirm.

Finally C. R. Austrian (14) by taking the blood of a patient who gave a marked tuberculin reaction, obtained typical anaphylactic symptoms in guinea-pigs inoculated with the blood intraperitoneally. The reacting material used was a specially prepared emulsion of pulverised Tubercle bacilli. He obtained typical anaphylactic symptoms and characteristic post mortem appearances.

Finally Helmholz (15) stated that tuberculous guinea-pigs gave a positive v. Pirquet's reaction. He also said that the blood of such guinea-pigs could confer passive hypersensitiveness to normal animals and that symbiosis with infected animals conferred the same. The cutaneous reactions did not occur with a single dose but after a series of doses given before and after the inoculation of the serum so that they might just as well have been due to Arthus' Phenomenon.

In these experiments it was attempted to obtain:

1. Active sensitisation by Tubercle bacilli, and to test these animals
   (a) for typical anaphylactic shock,
   (b) for temperature reaction,
   (c) for cutaneous reactions.
2. Passive sensitisation with isogenous tissues:
   (a) blood or serum of sensitised animals or animal suffering from tuberculosis,
   (b) with the tissues of the same,
   (c) testing for typical anaphylactic shock and temperature reactions.
3. Passive sensitisation with heterogenous tissues:
   (a) human blood,
   (b) human tissues.
4. Also to study the effect of a reacting dose of tuberculin on tubercular guinea-pigs.

1. Active sensitisation.

Guinea-pigs were inoculated intraperitoneally with an emulsion containing .02 gr. of dried Tubercle bacilli made by emulsifying the pulverised Tubercle bacilli obtained from Meister, Lucius, Brüning & Co. The whole was sterilised at 60° C for 1 hour and inoculated intraperitoneally. The guinea-pigs inoculated did not develop any symptoms.

After 3—4 weeks they were tested either by inoculating B.E. 5 mgr. intravenously into the anaesthetised animal, or intra-peritoneally or subcutaneously without anaesthetic.

Those that were inoculated intravenously mostly died acutely, some even before the needle could be withdrawn from the vein.

The animals developed convulsions, cyanosis, respiratory spasm, loss of corneal reflex and died rapidly. Post mortem examination showed typical emphysema of the lungs, the lungs meeting over the heart in front, slow coagulation of the blood, continuance of heart pulsation for a long time after death. In a few cases death was slower and there was a great fall of temperature, tremors, clonic convulsions, paresis etc.

In those inoculated intraperitoneally the symptoms were much slower but typical.

The first effect of the inoculation of the 5 mgr. B.E. intraperitoneally was to produce a train of symptoms which occurs in normal as well as in sensitised animals. The animals became very restless, made a peculiar squeaking noise and a jumping spasm or ran round the cage.

This only lasted a short time and was not characteristic of tuber-culin inoculations. It occurs with any inoculation into the peritoneal cavity except with normal saline or Ringers fluid. Thus it occurs with Aqua distillata, hypertonic salines, carbon etc.

There was also in the case of the tuberculin inoculation into a healthy animal a slight fall of temperature from 102°— 103° F. to 99° F. or so, but recovery was fairly rapid.

When however a dose of tuberculin was inoculated into a sensitised animal the symptoms above described were much more marked, and the animal got in addition the typical phenomena, fall of temperature rapidly to below 94° F., paresis, ruffling of the coat, tonic and clonic spasm and death. Death either occurred from asphyxia with typical distended lungs, or in other cases it appeared to be purely paralytic and the typical pulmonary condition was not seen.

The peritoneum was intensely hyperaemic: there were frequently haemorrhages into organs. In some cases great hyperaemia of parts of the intestines developed, affecting chiefly the small at other times the large intestine.

The blood was dark, coagulation greatly delayed and if the animal was killed before it would have died, then there was evidence of low blood pressure scarcely any blood being obtainable.

All stages could therefore be traced from a typical acute anaphylactic death, slower death but with typical pulmonary appearances to the forms where pulmonary post mortem appearances were not characteristic. Here it must be remarked that occasionally with acute death, the death occurred so rapidly that the lungs were only slightly distended. This has been noted in acute anaphylactic death from other methods of sensitisation as well, e. g. egg albumen sensitised guinea-pigs.

Table I.

Number and Weight	Dose	Interval	Reacting dose, remarks, etc.
T.A. 1 350 gr.	.02 gr. pulverised Tubercle bacilli i.p.	26 days	5 mgr. B.E. i.v. Animal died with respiratory spasm just as the injection was completed. P.M. Emphysema, pulsating heart.
T.A. 2 320 gr.	idem	26 ,,	3 mgr. B.E. i.v. Paralysis, respiratory spasms, Cheyne Stokes, Temp. below 94° F. Clonic spasms, died during night.
T.A. 3 400 gr.	,.	28 ,,	5 mgr. B.E. i.v. Cheyne Stokes, loss of corneal reflexes, cessation of respiration. Cyanosis. Convulsions. Typical P.M.
T.A. 4 318 gr.	,,	28 ,,	5 mgr. B.E. i.v. Dead before the whole amount was injected. P.M. Slight permanent emphysema. Heart beating.
T.A. 5 290 gr.	,,	28 ,,	5 mgr. B.E. i.p. Movements as described. Temp. below 94° F. in 10 mins. Ruffling of coat, paresis. Clonic spasms, respiratory rapidity. Death 3 hrs. Emphysema.
T.A. 6 312 gr.	,,	35 ,,	5 mgr. i.p. Peritoneal irritation. Fall of temperature, paresis, clonic spasms; death; lungs not much distended. Intestine very hyperemic especially small, patchy.
T.A. 7 408 gr.	,,	35 ,,	5 mgr. subcutaneously. Fall of temperature to 94° F., paresis marked, defecation, urination. Ruffling coat. Death during night. No typical P.M. appearances.
T.A. 8 315 gr.	,,	42 ,,	5 mgr. i.p. Same as T.A. 5.
T.A. 9 270 gr.	,,	42 ,,	10 mgr. subcutaneously. Fall of temperature, paresis, clonic spasms. Lungs emphysematous. Death in about 4 hrs.
T.A. 10 420 gr.	,,	42 ,.	5 mgr. i.v. Death in 10 minutes. Cheyne Stokes, respiratory spasm, fall of temperature below 94° F. Cyanosis, marked emphysema.

From the above results it will be seen:

1) That active hypersensitiveness to Tubercle bacilli can be induced by inoculation with a sufficient dose of pulverised dead Tubercle bacilli; as was also shown by F r i e d - b e r g e r (16).

2) That Bacillary emulsion will act as the reacting substance.

The symptoms produced were typical of anaphylaxis but further it must be remembered that the P.M. appearances were not always characteristic. This does not militate against hypersensitiveness being the cause of death, since with guinea-pigs sensitised with egg albumen the P.M. appearances vary in the same way; in very acute death there may not be time enough for the development of very marked emphysema and in the very slow ones the death appears to be more paralytic and due to loss of heat and toxicity so that the lung condition is not always typical.

With intraperitoneal injections there was always marked hyperaemia of the peritoneum and the cavity frequently contained large amounts of fluid.

It was seen by previous experiment that with guinea-pigs 10 mgr. Bacillary Emulsion was not fatal given intraperitoneally and that 5 mgr. to 15 mgr. was not fatal intravenously to guinea-pigs of 300—400 gr. 15 mgr. occasionally was so. There always was a fall of temperature with these doses.

Temperature reactions with actively hyper-sensitive guinea-pigs.

It was found by inoculating sensitised guinea-pigs with varying doses of bacillary emulsion that there was a mean which produced no rise of temperature. larger doses produced a fall, smaller a rise of temperature. The doseage varied somewhat with the size of the animal, the initial sensitising dose, and the period elapsing between initial and reacting doses.

Thus in sensitised animals 0.1 mgr. frequently produced no effect, smaller doses a marked rise, larger doses a fall of temperature.

Thus T.A. 11. Intraperitoneally 0.1 mgr. B.E. (1 month after .02 gr. Tub. B). Weight 280 gr.

Inoculated 2 pm. 102.8° F.	Inoculated 5 pm. 103.2° F.
3 „ 101.8	6 „ 102.8
4 „ 102.2	8 „ 102.6

T.A. 12. Same as above. .01 mgr. B.E. i.p. reacting dose. 32 days after inoculation with .02 gr. Tub. B. Weight 240 gr.

*2 pm. 102.0° F.	7 pm. 105.4° F.
3 „ 103.0	8 „ 103.4
5 „ 105.8	10 „ 102.0

T.A. 13. Same as before. .001 mgr. B.E. i.p. reacting dose. 32 days after inoculation with .02 gr. Tub. B. Weight 280 gr.

*2 pm. 102.4° F.	5 pm. 103.6° F.
3 „ 102.4	6 „ 102.8
4 „ 103.6	8 „ 102.0

T.A. 14. Same as series. .0001 mgr. B.E. i.p. reacting dose. Weight 325 gr. Temperature remained unaffected.

T.A. 15. Same as series. 2.5 mgr. B.E. i.p. reacting dose. 34 days after inoculation with .02 gr. Tub. B. Weight 360 gr.

*2 pm. 102.4° F.	6 pm. 99.4° F.
3 „ 100.6	8 „ 99.6
4 „ 99.2	10 „ 102.2

T.A. 16. Sames as series. .25 mgr. B.E. reacting dose i.p. 34 days after inoculation with .02 gr. Tub. B. Weight 360 gr.

*2⁰⁰ pm. 102.0° F.	5 pm. 105.2° F.
2³⁰ „ 103.0	6 „ 105.0
3⁰⁰ „ 103.8	8 „ 103.0
4⁰⁰ „ 104.8	

Guinea-pigs sensitised with 1 c.c. Old Tuberculin, reacting dose after 21 days.

O.T. G_1. 0.15 c.c. O.T. subcutaneously *11 am. 101.6° F.

12 „	100.6
1 pm.	102.0
2 „	101.8
3 „	102.8
4 „	101.0

O.T. G_2. 0.15 c.c. O.T. subcutaneously *11 am. 102.6° F.

12 „	103.6
2 pm.	105.6
3 „	104.6
5 „	103.4
7 „	102.4

O.T. G_3. 0.15 c.c. O.T. subcutaneously *2 pm. 102.8° F.

3 „	101.8
4 „	104.4
5 „	104.6
8 „	103.4
10 „	103.8

* = time of inoculation.

With small amounts of bacillary emulsion as sensitising dose, 2.5 mgr.

Gp. 1.   Weight 260 gr.   2.5 mgr. as reacting dose i.p. after 25 days.

*11^{30} am. 103,0° F.   3 pm. 98.0° F.
11^{45} „   97.4   5 „   95.0
1^{00} pm. 95.4   6 „   96.0
2^{00} „   98.0   10 „ 102.0

Gp. 2.   Weight 242 gr. as above sensitised with 2.5 mgr. B.E., reinoculated after 28 days with 1 mgr B.E.

*11^{00} am. 102.6° F.   2 pm. 100.6° F.
11^{30} „   100.2   3 „   101.2
11^{45} „   98.4   5 „   102.4
1^{00} „   98.4

Gp. 3.   Weight 231 gr.   0.1 mgr. B.E. reacting dose subcutaneously. Temperature rose without any initial fall from 102° F. to 106° F. in 5 hours.

Gp. 4.   0.001 mgr. B.E. reacting dose subutaneously.   Temperature rose from 102.4° F. to 103.6° F.

From these it becomes evident that guinea-pigs can be sensitised with old tuberculin or bacillary emulsions. The sensitising dose may be quite small .0025 gr. and these animals react with a fall of temperature with a moderate reacting dose and with a rise with a very small one. quite differently from the controls. This will be dealt with in a paper on temperature variations.

Controls.   Normal guinea-pigs.   Half hourly temperatures.

Gp. 280 gr. 10 mgr. B.E.	Gp. 260 gr. 2 mgr. B.E.	Gp. 236 gr. 2.5 mgr. B.E.	Gp. 238 gr. 1 mgr. B.E.	Gp. 271 gr. .01 mgr. B.E.	Gp. 197 gr. .001 mgr. B.E.
102.0° F.	102.8° F.	103.2° F.	102.6° F.	102.4° F.	103.2 F.
100.4	101.8	102.6	102.2	102.8	103.6
97.0	101.0	102.8	103.4	103.2	103.4
94.0	102.0	102.4	104.0	102.8	102.8
101.0	101.6	103.2	103.2	103.2	103.2
97.0	102.0	102.2	103.4	102.6	103.0
97.2	103.2		102.6	102.2	103.6
95.2	103.0				
95.4					

Cutaneous reactions.

Sensitised guinea-pigs were shaved over the gluteal region and on one side a drop of pure old tuberculin was placed, a scarification was made and the tuberculin allowed to dry in. In all cases nothing very definite was seen.

Intradermic.

A single dose of .02 c. c. of old tuberculin intradermically produced no changes which could be regarded as characteristic.

2. Passive sensitisation with isogenous tissues.

A. Blood of tuberculous guinea-pigs.

A series of guinea-pigs which had been inoculated with Tubercle bacilli were taken when they showed marked signs of tuberculosis. The blood was taken and in some cases allowed to clot, in others mixed with Sodium citrate or whipped. The serum or whole blood was inoculated either intraperitoneally or intravenously. After varying intervals a reacting dose of 2.5 to 5 mgr. of B.E. was injected either intraperitoneally or intravenously. It was found that the serum alone did not give such good results as the whole blood and that even for an intravenous sensitisation a fairly long interval was necessary to allow of marked sensitisation results to be noted.

Thus:

G.P. B_1, 210 grammes, serum of a tuberculous guinea-pig (nearly 10 c. c.) inoculated i.p. The effect was first to cause a fall from 102.4° F. to 98° F., then a rise up to 104° F. and by next morning it was normal.

48 hours after inoculation the reacting dose 5 mgr. B.E. i.p. The usual symptoms of peritoneal irritation occurred. After these had subsided the temperature fell to 96° F., there was ruffling of the hair, paresis, defecation, animal recovered.

G.P. B_2, 250 grammes, treated similarly with similar results.

G.P. B_3, 180 grammes, inoculated with the 10 c. c. of the citrated blood of a tuberculous guinea-pig. Animal became very ill, temperature fell to 95.6° F., rose subsequently to 105.2° F.

After 48 hours 2.5 mgr. B.E. i.p., after the irritation phenomena, temperature fell below 94° F., paresis, tremors, clonic spasms, dead in 5 hours. P.M. emphysema. Marked peritoneal injection, much fluid.

G.P. B_4, 294 grammes, the same as G.P. B_3, 5 mgr. B.E. reacting dose i.p., death in 3 hours. Inoculated 72 hours after injection of blood.

Other pigs were treated in the same way but did not die although they developed paresis, fall of temperature, etc.

G.P. B_5, 265 grammes. Inoculated i.p. with 8 c. c. of blood (whipped). Usual symptoms. Recovery to normal next morning.

Inoculated 5 mgr. B.E. i.p. 24 hours after previous inoculation. Peritoneal irritation. Temperature fell from 102.2° F. to 99.2° F. Recovery. No marked paresis, etc.

Control. Guinea-pigs inoculated i.p. with 5 c. c. of normal guinea-pigs blood. or serum.

48 hours after 5 mgr. B.E. Tuberculin i.p. Range of temperature 102.8° F. to 103.2° F., no paresis etc. Weight of pigs 260—280 grammes.

B. Intravenous inoculation.

Guinea-pigs were inoculated in the jugular vein under anaesthesia and aseptic precautions.

The reacting dose was also given intravenously.

G.P. V. 1, 5 c.c. blood i.v.

Loss of corneal reflexes, Cheyne Stokes breathing, prolonged paresis. Temperature fell to 100° F. from 102.4° F., then rose to 103.6° F.

24 hours after; 2.5 mgr. B.E. Temperature fell to 98.6° F., recovery rapid. Tremors, paresis. Animal recovered.

G.P. V. 2, 7 c.c. of blood. Symptoms as before.

24 hours later 5 mgr. B.E. i.v. Temporary cessation of respiration, spasmodic breathing, Cheyne Stokes, paresis, fall of temperature 95.8° F. Recovered.

G.P. V. 3, 7 c.c. of blood of tuberculous guinea-pig i.v. Produced rapid breathing, Cheyne Stokes phenomena, corneal reflexes absent, clonic spasms, prolonged paresis. Temperature fell from 103.2° F. to below 94° F. in 20 minutes in spite of animal being kept warm. After 4 hours the temperature rose to 105.6° F.

4 days after the pig was inoculated with 5 mgr. B.E. i.v. Death was almost instantaneous — there was a tonic convulsion, respiratory spasm. P.M. The lungs were emphysematous. Heart still beating.

G.P. V. 4, 5 c.c. blood of tuberculous guinea-pig, i.v. Animal very ill, paretic, clonic spasm, Cheyne Stokes breathing, temperature 96.2° F., 3 hours after 104.8° F.

4 days after. 2.5 mgr. B.E. Tetanic spasms, respiratory spasms, Cheyne Stokes breathing, defecation, paresis. Temperature below 94° F. Animal died during the night. P.M. emphysema of lungs.

G.P. V. 5, 180 grammes, 8 c.c. blood of tuberculous guinea-pig i.v. Train of symptoms as above.

5 mgr. B.E. 5 days after i.v. Animal died almost at once, spasms tonic and respiratory. P.M. emphysematous lungs.

G.P. V. 6, 320 grammes, 8 c.c. blood of tuberculous guinea-pig inoculated intraperitoneally. Fall of temperature to 96° F. from 102.8° F., rose to 105° F. next day.

4 days after 5 mgr. B.E. intravenously. Loss of corneal reflex, respiratory spasm, Cheyne Stokes, paresis, temperature below 94° F. Clonic spasms. Died in 5 hours. P.M. emphysematous lungs.

G.P. V. 7, 280 grammes, 7.5 c.c. blood of tuberculous guinea-pig i.p. Fall of temperature, subsequent rise to 104.4° F.

5 mgr. B.E. i.p. on 3rd day. Usual peritoneal irritation, fall of temperature to 94° F. from 102.4° F., paresis, defecation, tremors, recovery.

G.P. V. 8, 265 grammes, 5 c.c. serum of tuberculous guinea-pig i.v. Symptoms as recorded above, very little subsequent rise.

4 days later 5 mgr. B.E. i.v. Symptoms: fall of temperature 102.8° to 96.2° F., paresis, Cheyne Stokes, tremors. Recovery.

G.P. V. 9, 184 grammes. Same as above.

3 days later 5 mgr. B.E. i.v. Fall of temperature 103.2° F. to 95° F., prolonged paresis, Cheyne Stokes breathing, some respiratory spasm. Clonic spasms. Died during night. Lungs somewhat distended.

Thus it will be seen that after inoculating healthy guinea-pigs with the blood of guinea-pigs in the later stages of tubercular infection, typical anaphylactic phenomena may be produced by subsequent injection with Tuberculin B.E. The interval between the inoculation of the blood and the reacting dose apparently must be long. The blood acts better than the serum.

Another point of interest is the result of the primary inoculation, viz., the fall followed by the subsequent rise of temperature. This has been noted by us on injecting other tissues etc. and will be dealt with in another paper.

The drop of temperature due to shock after the operation alone was never so great as those noted here. Usually from 102° F. to about 99°—100° F.

C. Inoculation of guinea-pigs with the blood of actively sensitised pigs.

Three actively sensitised pigs' blood was taken and whipped. 5 c. c. of the blood was inoculated into each of three healthy guinea-pigs intravenously.

Gp. A, 180 gr.	Gp. B, 192 gr.	Gp. C, 186 gr.
Interval after inoculation		
3 days	5 days	7 days
Reacting dose		
2.5 mgr. B.E.	2.5 mgr. B.E.	5 mgr. B.E.
The animal was very ill, prolonged coma, paresis, Cheyne Stokes respirations, clonic spasms. Defecation. Temperature fell to 94° F., paresis, gradual recovery. Complete recovery.	Same as Gp. A	Animal died whilst being injected. Tonic spasms, cessation of respiration, few gasps. Typical P.M. phenomenon.

D. Inoculation of tissues of sensitised animals.

The livers of sensitised pigs were removed and ground up to a fine pulp and injected intraperitoneally.

Gp. 1	Gp. 2	Gp. 3
	Dose of tissue	
6 ccs.	6 ccs.	6 ccs.
	Interval after inoculation	
7 days	10 days	21 days
Reacting dose 5 mgr. i.v. Animal soon recovered. There was a little paresis. Temperature 96° F. After a few hours went up to 104.8° F.	Same as Gp. 1	This animal developed typical anaphylactic symptoms. With a reacting dose of 5 mgr. B.E. typical emphysema, etc. P.M.

In the case of egg albumen sensitised guinea-pigs, passive sensitisation with tissue of these pigs takes a long time if typical anaphylactic symptoms are to be produced, as will be seen in another paper. For temperature reactions the period is much shorter.

E. Inoculation of tissue from tuberculous guinea-pigs.

For intraperitoneal injection the tissues, liver, spleen or kidney, were removed aseptically and ground up in a sterile motar till a fine pulp was obtained which could pass through a fairly coarse hypodermic needle.

Intravenous injection was not successful owing to the primary toxicity of the tissue, a subject with which we are dealing in a later paper.

The dose that could be given intravenously was very small. For this purpose the organs were ground up, mixed with an equal quantity of normal saline and centrifuged. The supernatant fluid was used.

Intraperitoneal inoculation. Reacting dose i.v.

	Quantity	Interval	Reacting dose	Result
Gp. T. 1	5 c.c. liver mush.	7 days	5 mgr. B.E.	Cheyne Stokes, paresis, clonic spasms. Loss of corneal reflexes. Temp. below 94° F. Death 3 hrs. P.M. emphysema.

	Quantity	Interval	Reacting dose	Result
Gp. T. 2 250 gr.	3 c. c. liver mush.	7 days	5 mgr. B.E.	Death in 5'. Respiratory spasms, convulsions. P.M. emphysema, etc.
Gp. T. 3	3 c.c. same as 2.	7 ,,	,,	Cheyne Stokes, clonic spasms, paresis. Temp. below 94° F. Death in 1 hr. Lungs pale emphysematous.
Gp. T. 4	2 c.c.	3 ,,	,,	Paresis, fall of temperature below 94° F., recovery.
Gp. T. 5	5 c.c.	4 ,,	,,	Same as No. 4.

Intraperitoneal inoculation. Reacting dose intraperitoneally. The reacting dose was given 48 hours after inoculation.

Gp. T. 6 320 gr. 2 c.c. liver 101.6° F. 2.5 mgr. B.E.	Gp. T. 7 280 gr. 1 c.c. liver 102.2° F. .1 mgr. B.E.	Gp. T. 8 400 gr. 5 c.c. liver 101.6° F. .6 c.c. Old Tub.	Gp. T. 9 335 gr. 2 c.c. spleen 102.4° F. 2.5 mgr. B.E.	Gp. T. 10 1 c.c. spleen 102° F. 2.5 mgr. B.E.
Temperature rose in 4½ hours to 105.4° F.	no rise	Temperature fell in 1 hour to below 94° F.	Temperature rose in 6 hours to 105.2° F.	Temperature fell to 100° F., then rose to 103° F.

After the primary irritation symptoms had passed off there was in all some paresis, tremor, occasional respiratory spasm. All recovered.

Control: Gp. .6 c.c. old tuberculin.

The temperature fell from 101.4° F. to below 96° F. The fall was much slower than the others, and the rise was over sooner. The temperature of 96° F. was 2 hours later than, and the temperature had recovered to normal about 2 hours before the others inoculated with tubercular tissue.

Further.

Gp. T. 11.	Gp. T. 12.	Gp. T. 13.	Gp. T. 14.
2 c.c. mush of spleen and livers of tuberculous guinea-pigs. Usual symptoms. 72 hours after i.p.			
2.5 mgr. B.E.	1 mgr. B.E.	.1 mgr. B.E.	.5 mgr. B.E.
Temperature fell from 102.4° F. to 101.0 F., rose to 104.8° F. Paresis, tremors. Recovery.	No effect	From 102.8° F. to 105.8° F.	102.2° F. to 94° F. in 1 hour rose subsequently to 104.8° F. after 6 hours.

The following controls were made since it had been noted in some experiments to be dealt with in another paper that after a guinea-pig had been inoculated with a normal tissue emulsion, injection of a small dose of egg albumen was followed by a variation in temperature rise or fall according to the relative amount of tissue primarily inoculated and the dose of egg albumen.

Guinea-pigs inoculated with 2 c.c. of normal liver or serum. 72 hours later B.E. was inoculated i.p.

Hourly temperatures.

Gp. 1 5 mgr. B.E.	Gp. 2 2.5 mgr. B.E.	Gp. 3 1 mgr. B.E.	Gp. 4. 2 c.c. serum 5 mgr. B.E.
*102.4° F.	*103.0° F.	*102.2° F.	*102.6° F.
97.4	99.0	103.2	97.4
99.0	100.8	104.6	97.8
101.2	102.2	103.2	100.2
102.6	103.2	103.0	104.6
102.6	104.2	103.2	103.2
102.2	103.0	102.6	103.2

In some others, intravenous injection was performed but anaphylactic symptoms were never observed.

Thus it will be noted that there is not much difference between the normal and tuberculous tissues with regard to temperature effects. This may be due to the fact that the tuberculous tissues contain Tubercle bacilli and so a large amount of the enzyme or antibody is bound by them.

3. Inoculation of blood from patients with marked hypersensitiveness to tuberculin.

The blood used in the first of this series of experiments was from a patient suffering from chronic pulmonary and arthritic tuberculosis.

He reacted well to Tuberculin.

Three guinea-pigs were inoculated i.p. with 10 c. c. each of a mixture of equal parts of blood and Sodium citrate (1.5%) solution. After 24 hours they were re-injected intravenously.

Weight	G.H. 1 280 gr.	G.H. 2 265 gr.	G.H. 3 292 gr.
Reacting dose	.02 gr. pulverised Tubercle Bacilli	5 mgr. B.E.	0.02 gr. Egg albumen
*Temp. 11^{30}	102.0° F.	102.4° F.	102.6° F.
11^{45}	100.0	100.0	
12	105.0	102.0	100.0
1	106.0	105.0	102.0
3	105.4	106.0	102.2
7	102.6	105.2	102.0
10		102.8	

There was paresis, clonic spasms, stridor, urination etc. after the inoculation in G.H. 1 and 2.

The next series was with the blood from another patient who gave a violent tuberculin reaction. The blood was treated as before.

G.H. 4, 300 gr. 15 c. c. of mixture i.v.	G.H. 5, 280 gr. 10 c. c. of mixture i.v.
3 days later reacting dose was inoculated i.v.	
5 mgr. B.E.	5 mgr. B.E.
Animal died with respiratory spasm and tonic convulsions at end of injection. Typical lung condition.	Prolonged comatose condition, loss of corneal reflexes, clonic and tonic spasms, respiratory stridor. Temperature below 94° F. Died in 2 hours. Typical lung condition.

G.H. 6. Weight 300 gr., inoculated I. V. with 5 c. c. of the blood of a patient who was very sensitive to tuberculin. 50 hours after, 5 mgr B.E. inoculated intravenously.

Cheyne Stokes phenomenon, long lasting comatose condition, corneal reflexes very slight, Incontinence. Temperature below 94° F. Clonic convulsions.

Died during the night. No emphysema. Marked hyperaemia of intestines, especially the small.

G.H. 7. Inoculated with the blood of another patient sensitive to tuberculin 5 c.c. 36 hours after inoculation 2.5 mgr. B.E. given i.v.

Temperature 102.2° F. fell to 98.4° F. No convulsions, jerky breathing, paresis, incontinence. In one hour and a half the temperature had risen to 105.2° F. Recovery.

The above experiments show that occasionally true ana-phylatcic symptoms can be produced by passively sensitising guinea-pigs with the blood of tubercular patients giving a marked tuberculin reaction.

The classical symptoms and appearances may be obtained under suitable conditions.

It however remains to be proved if any stress can be laid on the rise of temperature obtained in some cases. For this the following three controls were made.

	G.P. S. 1 260 gr.	G.P. S. 2 224 gr.	G.P. S. 3 230 gr.
	5 c. c. of sheep's serum i.p. into each. 72 hours after, reacting dose i.v.		
	.02 gr. Tubercle B.	5 mgr. B.E.	.02 gr. Egg albumen
*11 am.	102.0° F.	102.4° F.	102.2° F.
11[30] „	100.0	99.2	97.2
1 pm.	102.0	102.0	97.2
2 „	104.0	103.6	100.0
3 „	104.6	104.0	102.0
4 „	105.0	104.2	104.8
5 „	103.0	103.0	104.0

Here again a rise of temperature is produced in guinea-pigs inoculated with a foreign normal serum. The rise is however much slower, taking 3—4 hours to occur, whereas with serum from tuberculous patients the rise occurs in half an hour to one and a half hours.

Again inoculation with small quantities of serum from tuberculous patients followed soon after by inoculation with tuberculin produced in some guinea-pigs a rise of temperature, in others a fall.

It is true that normal serum may occasionally also produce a rise of temperature under similar conditions but it does so infrequently. A fall has, however, never been noted. 0.4 to 0.8 c. c. of the serum were inoculated subcutaneously followed by a similar quantity of tuberculin (1 in 10). The injections were usually made into opposite thighs. Occasionally the Tuberculin was inoculated first. In all the experiments the animals were kept well fed. It was found that the temperature was constant either when the animals were fed or starved. Want of food, however, though the temperature

was constant, apparently prevented a reaction occurring. Starved animals never had a rise of temperature, though fed animals gave a rise with the same serum.

The chart shows the temperature effects obtained with the small doses described above. A, B. are controls.
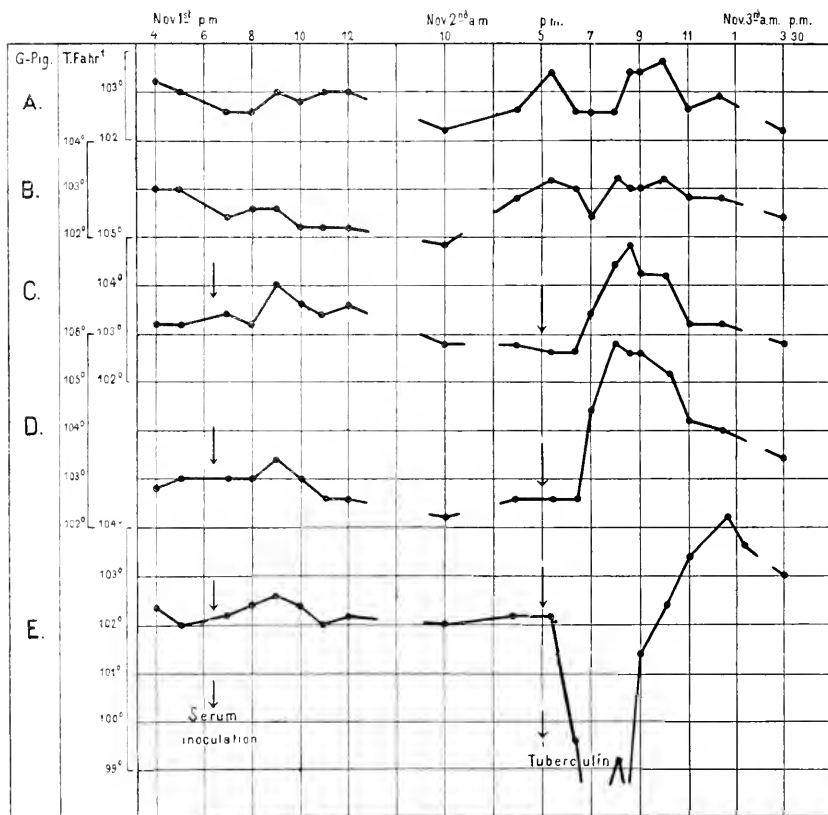
Curve.

4. Inoculation with tissues from cases of tuberculosis.

A. Lung from case of miliary tuberculosis, ground up with glass, mixed with equal quantity of saline, allowed to extract for 3 hours at room temperature. Centrifuged. Inoculated i.p. 2 c.c. were inoculated.

The animal always got symptoms of toxicity with a fall of temperature followed by a rise.

After 72 hours the following reacting doses were given.

	G.H.T. 1 .4 c. c. O.T.	G.H.T. 2 .6 c.c. O.T.	G.H.T. 3 2.5 mgr. B.E.	Control .6 c. c. O.T.
		intraperitoneally		
*11³⁰	101.4° F.	102.6° F.	101.8° F.	101.4° F.
11⁴⁰	98.4	101.2	97.4	99.0
12³⁰	101.6	98.4	94.0	96.0
2	103.0	103.6	94.0	99.4
4	102.6	103.8	96.0	101.2
5	102.0	103.8	97.8	102.0
6		102.8	101.0	101.2

B. Lungs and spleen from a case of chronic tuberculosis with acute miliary terminal infection. Ground up as before separately. 5 c. c. of fluid injected i.p.

72 hours after intravenously reacting dose.

	lung		spleen	
	G.H.T. 4 240 grammes 5 mgr. B.E.	G.H.T. 5 185 grammes 1 mgr. B.E.	G.H.T. 6 210 grammes 2.5 mgr. B.E.	G.H.T. 7 204 grammes 5 mgr. B.E.
*12	101.2° F.	102.4° F.	102.0° F.	101.8° F.
12³⁰ pm.	94.0	98.0	97.8	Died during injection. Tonic convulsions. Respiratory spasm.
1	94.0	103.2	94.0	
2	94.0	104.8	95.8	
4	94.0	105.2	100.2	
6	Death, paresis, clonic spasms, stridor, P.M. lungs emphysematous	105.0	103.4	
7		103.4	105.4	
10			103.0	
			paresis, spasms	

G.H.T. 8 and 9. Same tissue. I.p. inoculation 5 mgr. B.E. Fall of temperature, paresis, death during night.

P.M. lungs not typical.

5. Inoculation of Tubercular guinea-pigs with tuberculin.

A. Intraperitoneally.

1. 5 mgr. B.E. into tubercular guinea-pig.

Temperature rapidly fell from 101.8° F. to below 94° F. Animal at first had the signs of peritoneal irritation. Later paresis, jerky breathing, tense tender abdomen. Died during night. No emphysema. Small intestine very hyperaemic.

The same dose inoculated into others with similar results.

B. Intravenously.

5 mgr. B.E. inoculated i.v. into tuberculous guinea-pigs.

The animal remained comatose for nearly three hours, temperature below 94° F. Corneal reflexes gone. Cheyne Stokes breathing, cyanosis,

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clonic convulsions. Slight recovery. Animal died in 8 hours. No em-
physema. Hyperaemic small intestines.

Several other pigs were treated in the above way with similar results.

6. v. Pirquet's reaction in tubercular guinea-pigs.

No result has been noted in several cases.

Tuberculous guinea-pigs frequently gave a marked cuta-
neous reaction when an intradermic inoculation of Old Tuber-
culin or Bacillary emulsion was made.

The seat of inoculation became a large red infiltrated area
with occasional vesicles and the pigs developed a temperature
reaction ranging from 2—3 degrees. The reaction was usually
at its height about 16—24 hours after the inoculation.

Zusammenfassung.

Die Arbeit ergibt:

1) daß Meerschweinchen durch Inokulation von fein ge-
pulverten Tuberkelbacillen überempfindlich gemacht werden
konnten und dann typische anaphylaktische Erscheinungen
zeigten [vgl. auch Friedberger (16)].

2) daß die Ueberempfindlichkeit passiv auf Meerschwein-
chen übertragen werden konnte durch die Inokulation von
Blut oder Geweben eines aktiv-überempfindlichen Meer-
schweinchens;

3) daß Meerschweinchen, die mit dem Blute hochgradigen
tuberkulinempfindlicher tuberkulöser Patienten injiziert waren,
überempfindlich gegen Tuberkulin wurden. Dies gelang am
besten mit dem Blute.

4) In derselben Weise konnten Meerschweinchen mit tuber-
kulösen Geweben menschlicher Herkunft überempfindlich ge-
macht werden.

5) In ähnlicher Weise konnte man Meerschweinchen über-
empfindlich machen mit dem Blute oder Geweben von tuber-
kulösen Meerschweinchen.

6) Mit abgepaßten Dosen Tuberkulins konnte man entweder
Fieber oder Temperatursenkung bei aktiv-überempfindlichen
Meerschweinchen erzielen.

7) In ähnlicher Weise konnte man dasselbe erreichen bei
Meerschweinchen, die durch homogene oder heterogene Gewebe
überempfindlich gemacht waren.

Die Temperaturveränderungen in solchen Fällen waren nicht so sehr charakteristisch. Der Grund dafür liegt wohl darin, daß die injizierten Gewebe reich an Tuberkelbacillen waren und so wurde viel von dem spezifischen Antikörper dadurch gebunden. Typische Anaphylaxie wurde aber doch erzielt. Mit denselben Quantitäten Tuberkulins tritt der Unterschied zwischen normalen und aktiv-überempfindlichen Meerschweinchen sehr zutage.

8) Es gelang nie eine kutane Reaktion bei überempfindlichen Meerschweinchen zu erzielen.

Durch diesen Versuch ist es offenbar, daß der reagierende Antikörper, der mit Tuberkulin in tuberkulösen Patienten die Reaktion, Fieber usw. hervorruft, identisch ist mit dem, der in Meerschweinchen, die aktive oder übertragene Ueberempfindlichkeit besitzen, Anaphylaxie und Temperaturveränderungen verursacht. Dieser Antikörper ist auch in tuberkulösen Meerschweinchen vorhanden. Die Ueberempfindlichkeit kann an Meerschweinchen übertragen werden durch das Einspritzen des Blutes und der Gewebe solch tuberkulöser Patienten.

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A PRELIMINARY COMMUNICATION

ON

THE PATHOGENICITY AND VIRULENCE OF BACTERIA

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A PRELIMINARY COMMUNICATION

ON

THE PATHOGENICITY AND VIRULENCE
OF BACTERIA.[1]

As much of the work on which this paper is based has not yet been published it is necessary briefly to review the work in order to bring out the argument clearly. First, then, we must consider the mechanism of fever production.

Friedberger showed that in animals which have been sensitised with serum (for the demonstration of anaphylaxis) a much smaller dose of the protein is necessary for the production of temperature variations than is necessary in unsensitised animals. He also showed that in the early stages after sensitising an animal a further dose of a protein will produce a rise of temperature. but later on the *same* dose will produce a fall of temperature. Finally, he showed that if anaphylotoxin be prepared *in vitro*, a small dose injected into an animal will produce a rise of temperature, a larger dose a fall. From these observations he concluded that these various effects were due to the formation of anaphylotoxin produced *in vivo* on the one hand and *in vitro* on the other, and that the various effects depended on the amount exhibited.

Vaughan and Wheeler have shown that repeated doses of protein or bacteria produce temperature variations, the type of variation depending on the dose and frequency of inoculation. They consider that protein and bacteria contain a preformed toxic molecule.

Hort and Penfold have shown that temperature variations occur in animals when these are inoculated with certain bacteria. They consider that the temperature variations are due to a substance they designate pyrogen, which substance is supposed to be liberated from the medium on which the bacteria are grown.

We have been able to show the following.

1. Given a sufficiency of ferment in an animal, varying

quantities of protein or bacteria will produce, when injected, the following conditions :—

(a) A sufficiently small dose = no temperature variation.
(b) A larger dose = a temperature rise.
(c) ,, ,, = a greater rise.
(d) ,, ,, = less temperature rise.
(e) ,, ,, = no temperature variation.
(f) ,. .. = a temperature fall.
(g) ,, ,, = a greater fall followed by death.
(h) ,, .. = acute death, so-called anaphylaxis.

If, however, there is insufficient ferment present to start with, acute anaphylaxis can never be produced, and so on.

2. Proteolytic degradation bodies, so-called anaphylotoxin, manufactured *in vitro* produce effects parallel to the above according to the dose.

3. That by producing varying stages of anti-anaphylaxis (that is to say, the condition following the anaphylactic shock in which recovery has taken place), the conditions following a further dose depend on the amount of ferment used up by the first dose. Friedberger came to similar conclusions from his work. For example, if all the ferment is used up by the first dose the second dose produces no temperature variation. If most of the ferment is used up the second dose produces a temperature rise. If little ferment is used up the second dose produces a temperature fall.

4. By inoculating the tissues of animals sensitised to protein or bacteria into a normal animal, that these passively sensitised animals acquire the power of developing temperature variations after injection of the specific protein.

And we were able to show that if the amount of ferment—i.e., the sensitised tissue injected—were kept constant, temperature manifestations varied inversely with the amount of the protein subsequently injected, and by keeping the protein constant and the ferment variable similar results were obtained. Also, if normal tissues of animals were injected into normal animals, these animals developed the power of giving temperature variations with smaller doses of any protein than normal animals, this power being due to an increase in the normal ferments, specific or non-specific.

From these observations we have been able to deduce :—
That temperature variations are due to the interaction of the substance injected and the ferments present normal or induced. That the substance which gives rise to the temperature variations is an early degradation product of proteolytic disintegration of the injected substance. That the rise and fall are both due to the same substance and not different stages of degradation of this substance, but to its

rate of accumulation. The substance in large amounts produces a fall of temperature, in small amounts a rise ; so that the results depend on the relative amounts of substance injected and ferment present. If, then, there is sufficient ferment present, any stage can be produced from a single dose, according to its size, from a temperature raising effect, through a temperature depressing, through so-called anaphylaxis to the acute Auer Lewis phenomenon or acute anaphylaxis.

The toxicity of bacteria not possessing an exotoxin was formerly considered to be wholly due to the liberation of an endotoxin. Friedberger considers that toxicity is due to the formation of anaphylotoxin from the endotoxin, but does not absolutely deny the possibility of the endotoxin being directly toxic. Now, the views held at present with regard to the endotoxin are that it is (1) a toxic substance secreted in the animal body ; (2) a preformed toxic molecule which is liberated by breaking up of the bacterial cell (*a*) in the animal body by antibodies, (*b*) *in vitro* by alcoholic potash. (*c*) *in vitro* by watery potash, (*d*) *in vitro* by freezing and thawing or by freezing and grinding.

We have been able to show that the so-called endotoxin is really the toxic proteolytic degradation bodies liberated from the bacterial protoplasm by the action of the tissue ferments, and that accumulation of this body in bacterial infection is the cause of the symptoms and death, and is the same for all bacteria, and that this is the same substance obtained by Friedberger *in vitro* or from the peritoneal cavity, using the peritoneal cavity as a test-tube.

We conceive that the toxicity of a bacterium depends upon (1) the ease with which its protoplasm is accessible to ferment action ; (2) the nature and amount of ferment present. Thus, if a bacterium is fragile, the ferments present can attack the protoplasm easily, the toxic substance is liberated readily, and the symptoms depend on the amount of accumulated toxin at any given moment. On the other hand, if the bacterium is tough, for example, the tubercle bacillus with its fatty capsule, the ferments can only act on it very slowly, and consequently the rate of production of toxin is very much slower. Again, within limits, an increase in the ferment will increase the rate of liberation of toxic material from the bacterial protoplasm.

It is said that an animal dying from any form of bacterial infection is supposed to die from the specific poison i.e., the endotoxin. Now we have been able to show that the blood of these animals contains an intensely toxic substance, which when inoculated into guinea-pigs intravenously in doses of from 5 c.c. to 10 c.c. produces acute death with the typical symptoms and post-mortem appearances of proteolytic degradation body poisoning. We have obtained this syndrome with the blood of rabbits dying from chicken cholera, coli, danysz, dysentery, and phlei, and the blood of

guinea-pigs dying from staphylococcus, tubercle, proteus, and prodigiosus. We have also produced the same syndrome with the blood of animals which have died of toxæmia from the above-mentioned dead bacteria. The number of bacteria inoculated with the blood of these animals is extremely small, and is quite insufficient in itself to cause acute death of the type mentioned. In fact, we have shown that when bacteria are completely broken up by freezing and thawing or by grinding, so as to liberate the "endotoxin," death of this description only rarely occurs, and then with quantities of over 20 mgm. dry weight. We have succeeded in producing acute anaphylactic death with tubercle bacillary emulsion (B.E.), coli, and proteus. With all other organisms with large quantities intravenous injection causes delayed death (delayed anaphylaxis). The animal develops rigors, ruffling of the coat, fall of temperature below 94° F., paresis spreading from the posterior to the anterior extremities, and disordered respiration. On death the post-mortem changes are all the same—viz., congestion of the right side and veins, distended gall and urinary bladders, and a certain degree of lung distension. Now these symptoms and post-mortem appearances are identical with those produced by inoculation of egg albumin into egg sensitised guinea-pigs, in doses too small to cause acute death (or where the ferment is insufficient to cause acute death). Now we have noticed that guinea-pigs dying of any bacterial infection die with these same symptoms and post-mortem appearances. The results obtained by Arima with so-called typhoid toxins—i.e., the soluble and insoluble typhoid protoplasm—are identical with these. Vaughan and Wheeler have produced tissue changes in animals by the repeated inoculation of egg albumin which are exactly the same as those produced by bacterial infections.

Thus we see that the toxic substance liberated from bacteria in large quantities produces in normal animals symptoms of acute proteolytic degradation body poisoning, in smaller quantities great fall of temperature, paresis, rigors, &c., in smaller quantities still fever ; and that the so-called endotoxins only give rise to those symptoms when the various ferments have been able to produce the necessary accumulation of degradation bodies to give rise to the symptoms. In animal infection the difference between the symptoms produced by the different bacteria depends on the distribution, rate of multiplication, and consequent liberation of the degradation bodies. For example, a characteristic clinical picture may be obtained with certain bacteria due to local cumulative effects. In certain structures where the organism is normally present in large quantities, and is continually there undergoing proteolytic degradation—for example, in the intestines—we always note in coli infections intense hyperæmia of the mucous membrane and hyperæmia of Peyer's patches in guinea-pigs.

A similar condition was noted by Schittenhelm in dogs, by injection of hydrolytic degradation products of bacilli coli. The acute toxic material of Vaughan and Wheeler, Schittenhelm, &c., are really early hydrolytic cleavage products and not unaltered bacterial protoplasm.

Friedberger, in his paper on anaphylatoxin fever, drew attention to the similarity between certain features in the syndrome of bacterial infection and those produced by anaphylatoxin.

To summarise. 1. Endotoxin as originally understood does not exist. The bacterium does not liberate a primarily toxic substance. 2. The bacterial protoplasm itself is not directly toxic. 3. The bacterial protoplasm becomes toxic on exposure to ferments. 4. The degree of toxicity depends on the accessibility of bacterial protoplasm and concentration of ferment 5. As we shall show later, if the amount of ferment is very large, lysis occurs so rapidly that the bacterial protoplasm is broken down to non-toxic substances.

Now with regard to the ferment and its formation. Working on the early stages of the formation of a hæmolytic antibody in rabbits to human red cells, the development of the specific antibodies can be traced through the following stages from the panenzyme. Complement in its simplest form must be regarded as panenzyme, which will attack any form of protein, though slowly. In its earliest stage the specific ferment occurs in such a condition that when exposed to the specific antigen at $0°$ C. it combines with it, and it is found that the complement, which would otherwise activate sensitised homologous antigen, has been removed, but that the other complements are left free. This ferment is destroyed by heat at $56°$ C., and cannot be reactivated by the addition of fresh complement. The next stage is the development of a thermolabile amboceptor, which combines at $0°$ C. and does not fix complement in the cold and by itself will agglutinate. The final stage is the development of the thermostable amboceptor. In the normally occurring hæmolytic antibody (e.g., in rabbits to sheep's red cells) all three stages may be demonstrated to occur at the same time, and it seems that the younger the animal the less differentiated the ferment is. The antibodies to bacteria apparently go through the same stages, but it is only in certain cases that the whole process can be traced. Thus we consider that the complement is an enzyme, and the amboceptor is a kinase or coenzyme which activates and adjuvants the former.

From the above work we thought that organisms were not pathogenic because they produce endotoxin, but were pathogenic to animals because the animals had ferments which were capable of acting on the bacteria so as to cause an accumulation of proteolytic degradation bodies, which would inhibit phagocytosis and allow the bacteria to multiply.

With regard to phagocytosis we shall shortly publish a paper with Dr. Stanley Warren in which are shown the following : 1. Carbon particles and bacteria to which the animal has no ferments act as innocuous substances and are phagocytosed by the polymorphonuclear neutrophiles, and these in turn by endothelial cells.   2. In an animal which is immune from the presence of a large quantity of ferment the bacteria are very rapidly broken down beyond the toxic stage, and so are innocuous, and the usual sequence of phagocytosis occurs.   3. In an animal in which the ferments are unable to completely break down the bacterial protoplasm quickly enough the toxic proteolytic degradation bodies are liberated, and these act aggressively, inhibiting phagocytosis.   If these toxic bodies accumulate at a sufficient rate the animal dies and the endothelial cells do not appear in the exudate.   If, however, the toxic bodies do not accumulate so rapidly, the polymorphonuclear neutrophile cells, after a considerable increase in numbers, are able in time to phagocytose the bacteria, and eventually the usual sequence, though delayed, occurs.

So we would say that an animal is immune to a bacterium (1) if the bacterium is unacted on by the ferments and so remains innocuous, (2) if it is so rapidly broken up by the ferments present that its proteolytic degradation bodies are quickly reduced to non-toxic ones, and so it again becomes innocuous.   And an animal is susceptible to a bacterium if the ferments can split off from the bacterium toxic substances in such amount as to inhibit phagocytosis.   Thus to a given bacterium an animal may have very little ferment action, and little toxic substance will be split off to act aggressively, so that phagocytosis will occur and the animal will be unaffected.   If, however, the ferment activity is greater because there is more ferment, or because there is a specific ferment, or because the bacterium is more fragile, then toxic substances will be liberated in sufficient amount to act aggressively, so that phagocytosis will not occur, the bacteria will multiply, and septicæmia will ensue (or the ferment may destroy the bacterium, but may be present in insufficient amount to degrade the protoplasm sufficiently rapidly to render it non-toxic, so that these toxic substances liberated will kill the animal).   Further, if the ferment activity is still greater the bacteria will be rapidly degraded beyond the toxic stages, aggressive substances will not accumulate, phagocytosis will occur, and the animal will recover.

First, then, we will take organisms to which the ferment activity normally is very low, such, for example, as the bacillus mycoides (a soil organism superficially resembling the anthrax bacillus, but naturally incapable of growth at the body temperature and posessing flagella), the timothy grass bacillus, and the smegma bacillus.   These organisms, when injected into the animal body, produce in the case of

the bacillus mycoides no lesions (even when this organism is educated to grow at body temperature). In the case of the timothy grass bacillus a plastic peritonitis occurs with pseudo-tubercles, with massive doses in the guinea-pig, from which the animal recovers. The infection only proves fatal on the addition of butter, and only Rabinowitch has been able to pass the strain on subsequent inoculation ; other observers repeating her work have failed. The organism produces no disease in rabbits.

A series of guinea-pigs were inoculated with 20 mgm. dry weight of these organisms. In the case of mycoides, after a week it was found that the intraperitoneal inoculation of an agar slope of mycoides grown at 37° C. produced death of a sensitised guinea-pig in 60 hours. The post-mortem appearances were œdema of the abdominal wall, slightly turbid peritoneal effusion, enlargement and congestion of the spleen, liver, and kidneys, moderate distension of the lungs, engorgement of the right side and veins. The organism was recovered in pure culture from the œdema and peritoneal fluid, from the spleen, gall-bladder, urinary bladder, and heart's blood. Microscopically the organism was seen in the capillaries of the spleen and liver and was non-sporing. The post-mortem appearances were thus indistinguishable from those of anthrax.

With the timothy grass and the smegma bacilli an inoculation was made of one 24-hour glycerin agar slope intraperitoneally into each guinea-pig correspondingly sensitised one week previously. Death occurred in from ten days to a fortnight. The post-mortem appearances were emaciation and hair falling out, miliary tubercles throughout the body, some degree of plastic peritonitis in addition to the usual pseudo-tubercles that occur with the inoculation of these organisms into normal animals. The omentum was rolled up, infiltrated, and studded with tubercles. The organisms were recovered from the heart's blood in addition to other sources. The microscopical appearances were those of marked epithelioid reaction with the organisms in the lesions, and in the centre of some of the lesions typical granular necrosis. The post-mortem appearances were thus indistinguishable from those due to an intraperitoneal injection of tubercle bacilli.

Parallel to these is an experiment in which we were able to produce acute miliary tuberculosis in a rabbit with a very small quantity of human tubercle bacilli. The rabbit was inoculated with about 0·05 mgm. of human tubercle bacilli **14** days after sensitisation with 50 mgm. of killed pulverised tubercle bacilli. The rabbit died in one week. In a similar way Duval and Couret have shown that experimental leprosy lesions can only be produced in monkeys after previous inoculation with dead leprosy bacilli.

We found that the sensitive period for infection was from six to ten days after the sensitising dose. If, however, the

second inoculation is given to a sensitised animal after an interval of a fortnight instead of a week the animal recovers and does not develop the disease, unless a much larger second dose is given than in the above experiments. Later still the animal becomes so immune that the second dose, to produce any symptoms, has now to be so large that it is only capable of producing delayed toxic death, the animal not living long enough to develop septicæmia. The reason for this is that the ferment is increasing in quantity and is becoming more specialised as the length of time from the sensitising dose increases. And only by using the methods we are just coming to can septicæmic death be produced.

Secondly, we will consider organisms to which ferment activity is relatively high, so that the guinea-pigs are immune from this reason. Organisms of this description are Hoffmann's bacillus, sarcina, proteus Zenkeri, staphylococcus pyogenes aureus, streptococcus erysipelatis, and cyanogenus. We found that in trying to produce lesions with these organisms by the previous method we were unsuccessful, and in most of them the large initial doses of the bacilli, 10–20 mgm. dry weight, produced death from toxæmia, with occasional terminal coli, &c., infections. From this we concluded that the available ferment present was capable of rendering non-toxic relatively large quantities of bacteria. Such being the case, we thought that if by some means we could (1) prevent the ferment getting rapidly at the bacterium, or (2) delay ferment action, we should be able to produce septicæmia with these organisms ; for we should prevent the rapid breaking down of the bacteria, and so allow aggressive substances to be formed. The bacteria would then be able to multiply *in situ* until the available ferment was so reduced that the organisms would be able to pass into and multiply in the blood stream. To obtain this result we injected the bacteria in 15 and 30 per cent. gelatin, and 2, 3, and 5 per cent. saline. The gelatin was used with the idea of delaying the access of the ferment to the bacteria, and of keeping the degradation products formed in their immediate vicinity and so produce around them a state of ferment equilibrium. The bacteria, then, as a result of this could multiply. The viscosity of the gelatin would further tend to delay the advent of the phagocytes. The gelatin might be thought to be able to produce toxic results by itself, which we found not to occur, or in adjuvanting the toxic substances formed from the bacteria by degradation bodies from the gelatin itself. That this latter apparently is not the case can be seen from our experiments in which egg sensitised guinea-pigs, receiving a second dose of egg albumin, so as to produce a great fall of temperature lasting for hours, were not susceptible to several slopes of staphylococcus inoculated simultaneously, though degradation bodies from the egg must have been present.

The hypertonic saline, as has been shown by Friedberger and his co-workers, inhibits ferment action, and we conceived that by injecting hypertonic saline into the peritoneal cavity the ferment action would be delayed until the necessary dilution of the saline had occurred by osmosis. We will discuss the effect of hypertonic saline on the bacteria later. Working by these methods we were able to produce fatal septicæmia with all these organisms, but the amount of bacterial substance required was very different with the different bacteria. The less primarily toxic the bacterium was, the more was required to produce septicæmic death.

Except in so far as the gelatin method can be used for demonstrating that where large amounts of ferment are presumably present, the amounts of bacterial substance required to produce septicæmic death are correspondingly large, in the light of further work we do not consider the gelatin method a good one for proving immunity due to large quantities of ferments ; for we have been able to produce by this method, but not by the saline, acute septicæmic death with an unpassed mycoides (growing 37° C.). This can readily be explained. Friedberger was able to produce anaphylotoxin in the peritoneal cavity of guinea-pigs with any bacterium. We have noted that where large amounts of coagulated egg albumin are introduced into the peritoneal cavity toxic substances are formed from it, producing a fall of temperature. In the same way similar substances can be liberated from the bacillus mycoides, and in the viscid gelatin, zones of ferment equilibrium become established round the bacteria ; the ferment then is incapable of destroying them, and by the time the delayed phagocytes arrive at the bacterium the aggressive substances prevent phagocytosis and the organism is able to survive.

Thus we have proved that the pathogenicity of bacteria depends upon the activity of the ferments in the animal host. If there is no, or slight, activity the organism is non-pathogenic, if there is a high degree of activity again the bacteria are non-pathogenic ; and by either increasing or diminishing the ferment activity, as the case may be, the bacteria may be rendered pathogenic.

Now with regard to virulence of bacteria. This must be regarded as entirely an educative property acquired by the bacterium. Gal showed that bacteria could be rendered virulent by cultivation in the presence of an enzyme, such as the enzyme of yeast cells. He further showed that virulent bacteria could more readily undergo disintegration than non-virulent, and demonstrated a so-called antitryptic effect.

We have shown (1) that bacteria which are primarily non-pathogenic can, after passage through a sensitised animal, become so altered that they now produce disease in a normal animal—that is to say, they can be acted upon by the normal ferments so readily that sufficient aggressive

substances are formed ; (2) that organisms which have been obtained from the blood of septicæmic animals, which are normally immune owing to the high activity of the ferment, inoculated into normal animals, will produce disease and death ; and (3) that some organisms when they become virulent can develop a capsule. With regard to the first of these points we have been able to produce disease followed by death in normal animals after inoculating with passed bacillus mycoides, timothy grass bacillus, and smegma bacillus, not only in guinea-pigs in which the original passage was conducted, but also in rabbits and rats. In the case of the bacillus mycoides, it eventually became so virulent after several passages that one-twentieth of a 24-hours agar slope killed a normal guinea-pig weighing 300 grm. in about 36 hours. One-twentieth of an agar slope killed a rat in 24 hours, and half an agar slope killed a rabbit in 24 hours. Finally, 18 guinea-pigs which had been placed in cages in which other guinea-pigs had died from the disease, all died as the result of intestinal infection. It is interesting to note that one guinea-pig which was pregnant was found to have the bacillus mycoides in pure culture in the amniotic fluid. With regard to the timothy grass and smegma infections, the bacteria when isolated or when injected in the ground-up spleen produced in normal guinea-pigs death with miliary tuberculosis and enlargement of the lymphatic glands in the chest in from four to 20 days. The organism has, as a result of repeated passage, now become so virulent that septicæmic death will occur in four days.

The organisms when inoculated intraperitoneally into a rabbit in small quantity produce death in a week with general miliary tuberculosis, slight fibrinous peritonitis, and enlarged glands showing miliary tubercles in the chest. This is particularly important because lesions are not produced in the rabbit by the unpassed bacteria.

With regard to the second group of organisms, these, when passed, produce septicæmia with very small quantities without the aid of gelatin or hypertonic saline. It was found that the bacillus mycoides which ordinarily has flagella and no capsule in the animal body develops a capsule and loses its flagella when it becomes virulent.

We will first discuss the composition and function of the capsule. We conceive that the capsule is composed of extruded bacterial cytoplasm, which is extruded for the purpose of engaging the ferments and preventing them from reaching the bacterium itself, and causing its death and destruction. It appears to us that the mechanism is to produce a state of ferment equilibrium around the bacterium, so that the bacterium is shielded from the further action of the ferment and is able to grow and multiply. Whether this is successful or not depends upon the relative amount of bacterial protoplasm and ferment activity. We are aided

in this conception by the action of hypertonic saline, noted in our experiments. The hypertonic saline in addition to hindering the action of the ferments also appears to have an influence on the bacterium. The bacterium being in a hypertonic solution is subject to osmosis, the result of which is that diffusion of the bacterial cytoplasm occurs, thus forming a capsule in which the same condition of ferment equilibrium can be maintained in the presence of the weakly acting ferments.

In the case of the gelatin similar zones of equilibrium are maintained around the bacteria in the gelatin. The gelatin prevents rapid removal of the degradation bodies produced around the bacteria. It is conceivable also that the bacteria exude a little protoplasm into the surrounding medium which may be more soluble than the capsules ordinarily demonstrable. This is kept in position by the gelatin, so that the necessary equilibrium zone can be maintained. This is seen in the case of our experiments with the proteus Zenkeri, where an unpassed strain was injected in gelatin and in 5 per cent. saline. Seven agar slopes injected in 5 per cent. saline produced no result beyond a transitory fall of temperature, but four agar slopes in gelatin produced toxic death and eight slopes produced septicæmia. The difference in the two cases would appear to be due to the gelatin temporarily acting as a containing capsule preventing the removal of the aggressive substances.

We would conceive that exotoxin is really this capsule formation in an exaggerated degree, but differs in that the bacterium diffuses its protoplasm into the surrounding medium instead of retaining it in its immediate vicinity. And we regard exotoxin as soluble bacterial protoplasm which only becomes toxic on contact with ferment. The reason why we are led to conclude this is that with bacillus diphtheriæ and bacillus Hoffmann a septicæmia has never been produced. This appears to us to be due to the fact that zones of ferment equilibrium do not occur intimately around the bacterium, and so the ferment, which is apparently of high activity, is able to penetrate and kill the bacteria, the animal dying from toxæmia. The proof of the high ferment activity is that the guinea-pig can withstand large doses of these organisms if inoculated in the ordinary way, and that the animal does not take the disease after sensitisation. Now we have been able to obtain a Hoffmann and diphtheria septicæmic death by means of the gelatin and saline methods.

From this we conclude that by the gelatin method we were able to keep the exuded bacterial protoplasm in intimate contact with the bacterium, so that a zone of ferment equilibrium could be established round the bacterium, forming a protective sheath against the further action of the ferment. In the case of the saline, the inhibition of the ferment action and the exudation of the greater amount and the lessened

tendency to diffusion of the bacterial protoplasm will bring about the same result.

That these animals die from proteolytic degradation body poisoning can be demonstrated by the fact that the inoculation of their blood intravenously into a normal guinea-pig produces acute toxic death (acute anaphylaxis). This brings the diphtheria bacillus into line with the other bacteria. And it shows that death from bacteria possessing an exotoxin or not is always due to the same cause—i.e., proteolytic degradation body poisoning.

In order to further this view several points require explanation. How does toxin become toxoid? Toxins may be converted into toxoids by heat, by standing, by sunlight, and by drugs such as iodine. With regard to heat, if exotoxin is bacterial substance it will contain the autolytic ferment of the bacterium. Now, on moderate warmth or standing this ferment starts degrading the bacterial protoplasm, and after a time no further degradation can occur (unless the end-bodies are removed) owing to ferment equilibrium, so that at any time there will be present (1) unaltered bacterial protoplasm, which on inoculation can be converted into toxic early degradation bodies ; (2) early degradation bodies, which on further action are rendered non-toxic ; and (3) non-toxic end-bodies.

The much smaller amount of unaltered protoplasm is more rapidly attacked by the ferment present in the animal, so that the toxic bodies only tend to be present at any time in small amount, producing local changes at the seat of inoculation and no general poisoning. On this assumption we can also explain how it is that a toxoid can act as an antigen. Again, this explains why the fixation of complement occurs when toxin and antitoxin are added together, for we must consider the antitoxin as a co-enzyme or amboceptor.

Then, with regard to the difference between the L 0 and the L + dose, on the principle on which these are worked out, no account is taken of the normal active ferment present in the guinea-pig.

With regard to chemicals such as iodine converting the toxin into toxoid, we have the observations of Friedberger and Schittenhelm that iodised albumin can act as an absolutely foreign proteid to the homologous animal, so that iodine acting on bacterial protoplasm may so alter it that the ferments which could easily attack the ordinary toxin can now only very slowly act on the iodised "toxin." But as we know, iodised toxoid can produce antitoxin, that is, a ferment against the unaltered toxin ; this is parallel to the observation of Schittenhelm that guinea-pigs sensitised against iodised egg albumin can react not only to that but to plain egg albumin. This means that the newly evolved ferment can also degrade the non-iodised homologous proteid.

Though we have discussed so far pathogenicity and

virulence separately, yet we have come to the conclusion that they must be considered together. Thus an organism by passage may become so altered that it is able to infect and multiply in an animal in which there is no specific ferment. The mycoides could only become pathogenic in the first instance on inoculation into a sensitised animal—that is, an animal that has acquired a certain amount of specific ferment. After passage this organism is capable of producing disease in a normal animal—that is, an animal which only contains panenzyme. Hence we must conclude that the bacterium has become so altered that it can be attacked by the panenzyme at such a rate that sufficient aggressive substances are formed to prevent phagocytosis, and developed the property of extruding a capsule to form a protective zone in which ferment equilibrium occurs to prevent the enzyme from penetrating and destroying it. Thus we see that a bacterium which is virulent may also be pathogenic. The passed smegma and phlei are similar.

Now we must consider the bacteria which are not under ordinary circumstances pathogenic, and which do not become so when the ferment is raised against them by the production of specific antibodies. The first point we must discuss is the activity of the ferment. We have come to the conclusion that septicæmia is not produced by a process of general ferment equilibrium in the whole animal body ; but that septicæmia occurs if the relation between the quantity of bacterial protoplasm and the ferment activity is such that aggressive substances are formed from the bacterial protoplasm by the ferment in sufficient amount and remain as such long enough to inhibit phagocytosis.

Now first of all we can compare *in vivo* experiments with experiments carried out in the test-tube. From theoretical considerations the quantity of ferment only influences the rate of degradation, not the amount. So that *in vitro*, no matter how much ferment is present, ferment equilibrium eventually takes place and the same amount of the un-degraded material remains in the two cases. This would mean unaltered bacterial protoplasm. We know from experiments *in vitro* that under these conditions after ferment equilibrium has occurred the bacteria start to multiply again. Now, taking two guinea-pigs with the same quantity of ferment, if in one the ferment activity is unaffected and in the other the ferment activity is damped, and into each the same amount of living bacterial protoplasm is inoculated, ferment equilibrium should occur in both, and septicæmia, if it occurs in one should occur in the other, but at different times. But we find that where the ferment has been damped septicæmia occurs, and not in the other. Hence we must conclude that septicæmia is not produced by general ferment equilibrium in the animal body alone. Taking account also of rate of removal of end bodies in both cases, these are being gradually removed, in the one case more rapidly than

the other ; so that in both cases, theoretically, if the amount of ferment is sufficient, the primary substance should be completely broken down. Hence we must conclude that the occurrence of a septicæmia depends upon the presence at any given time and the maintenance of early degradation products sufficient to prevent phagocytosis. Where the ferment activity is great, the accumulation of the aggressive early degradation bodies is temporary, so that the inhibition of phagocytosis is only temporary, and this ceases directly the bodies are further degraded.

Finally there remains for discussion the fact that these organisms, which by our methods have produced septicæmia, are now able when directly inoculated into a normal animal, and in much smaller doses, to produce septicæmia. The fact that they can do so is a great argument against fermentative equilibrium being the sole cause of septicæmia.

Taking two normal animals and inoculating the same quantity of passed and unpassed bacteria, in the former septicæmia occurs, in the latter nothing. Here the factors are the same : the same activity, the same weight of bacterial protoplasm ; hence if septicæmia were solely due to general ferment equilibrium septicæmia should occur in both. Hence we conclude that the difference is due to the retention around the passed bacterium of bacterial protoplasm in various stages of degradation, forming on the one hand an aggressive shield against the phagocyte, and on the other against the ferment, so that the bacterium can multiply. Here again we believe that a bacterium which is virulent is so in virtue of its being able to exude some of its cytoplasm around itself and not into the surrounding medium, and we should expect that on these lines a diphtheria bacillus which became virulent would not produce soluble exotoxin, but keep its halo of bacterial substance around itself. That this is probably so is brought out by the well known observation that a very virulent diphtheria bacillus produces very little exotoxin.

Conclusions.

1. Ferments form an important normal mechanism of defence against bacterial invasion. The ferments performing this important function are : (*a*) the normal panenzyme, (*b*) the slightly differentiated specific enzyme, (*c*) the thermolabile specific coenzyme or amboceptor, and (*d*) the thermostable specific coenzyme or amboceptor. These last two adjuvant and accelerate the action of the ordinary enzyme. The action of the ferment is to bring about proteolytic digestion of the bacteria.

2. Exotoxins and endotoxins are bacterial protoplasm and

are not primarily toxic *per se*, but only become so when acted upon by the ferments.

3. The action of the ferments on the bacterial protoplasm is to produce toxic early proteolytic digestion bodies. These bodies, besides being toxic to the animal, are also aggressive in the sense of Bail i.e., are anti-phagocytic.

4. The action of this toxic substance, besides being aggressive, is to produce (*a*) in large amounts, death ; (*b*) in lesser amounts, fall of temperature ; and (*c*) in small amounts, fever. This substance is the cause of death in all bacterial infections.

5. The virulence of a bacterium is dependent upon the power of exuding around itself a zone of its cytoplasm, which remains in position and acts as a protective shield. The production of a zone of ferment equilibrium in this shield protects the bacterium itself from the penetration of the ferment. The shield thus acted upon is also aggressive to phagocytosis.

6. Pathogenicity is due to (*a*) the virulence of the bacterium, and (*b*) the relative activity of the ferment to the bacterium. Thus we should say that immunity is due to ferment action and phagocytosis—i.e., it is cellulo-humoral.

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The Variations in the Mucin Content of the Bulbo-Urethral Glands.[1]

By

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(With Plat. I.)

The bulbo-urethral glands are usually termed Cowper's glands in the male and Bartholin's glands in the female. The word mucin throughout this paper is applied to a substance or substances giving certain micro-chemical chemical reactions, chiefly those with thionin and mucicarmine, no chemical analysis of this substance has been made and therefore whether or not it is mucin in the strict chemical sense, depends on the specificity of these reactions; it can only be said that apparently identical reactions are given in organs e. g. the colon, where the substance is known to be true mucin.

It was found by Henle [5] that the ducts of Cowper's glands in both adult man and young infants were distended with an alcohol clotting substance, from this circumstance he concluded that the ducts acted as reservoirs for secretion and that the glands had no genital function. Later, Vitalis Müller [8] showed that both at birth and considerably before, the cells and contents of the acini in human glands of both sexes gave a red reaction with thionin similar to that of the cells in the rectum, but differing from the latter in fading sooner; no red colour

was seen in the ducts. Thomas [11] observed in human Bartholin's glands stained with muci-carmine, that part of the gland cells gave an intense mucin reaction and part none at all, while the secretion in the ducts gave a reddish yellow colour, he supposed that either the mucin in the cells was not secreted as such, or that the cells with no mucin secreted another substance, which so diluted the mucin as to give the secretion in the ducts the appearance he found: he considered the latter more probable.

The following observations have been chiefly made on the glands of the cat, guinea-pig and rat.

The glands are well marked in both sexes of the cat. In the guinea-pig and rat Bartholin's glands appear to be either vestigial or entirely absent, a rather remarkable circumstance considering the enormous development of Cowper's glands in these animals. The gland figured by Huguier [6] as the Bartholin's gland of the rat has a duct opening at the side of the clitoris and the histological structure of a sebaceous gland, it almost certainly has nothing to do with Bartholin's gland and corresponds to the preputial gland present in the male.

The glands were fixed in a sublimate-formol-acetic acid mixture and cut in paraffin. Before staining the excess of sublimate was removed from the sections with iodine and alcohol. In the great majority of cases muci-carmine was used for the demonstration of mucin, after the section had been stained with Mallory's iron haematoxylin, this appeared to be the best mucin reagent. In many cases sections were stained with thionin as well, and in a few of the earlier ones only this stain was used. When large quantities of mucin were present freshly made Weigert's elastic stain gave a grey coloration to it as well as to elastic fibres: this stain was occasionally used followed by lithium carmine to compare the amount of mucin in two glands where both contained large quantities.

I. Physiological Variations.

1. Bartholin's Glands in Oestrus.

Observations on this were confined entirely to the cat. The size of the gland in the adult animal varied from that of a hempseed to

that of a pea. It was surrounded by a capsule of striped muscle to which a branch of the pudic nerve could be traced.

Sections of the gland showed it to be composed of acini formed of a single layer of epithilium lying in a fibro-areolar stroma containing elastic fibres and plain muscle. The epithilial cells of the acini showed all gradations between two extreme types: (i) A tall columnar cell with a clear body, giving a marked mucin reaction, and possessing deeply stained, compressed nucleus at its base; this cell was sharply marked off from those on either side, especially when stained only with haematoxylin; and (ii) a cubical or flattened cell, giving no mucin reaction, consisting of a large, round, clearly stained nucleus surrounded by a small amount of faintly stained cytoplasm; the nucleus contained a well marked nucleolus and chromatin network; the separation between such cells was ill-defined. The cells in the same acinus might vary considerably, particularly in the degree of the mucin reaction, but the two extremes were not associated in the same acinus; they might, however, be seen in different acini of the same gland. Goblet cells were never found. The glands of different individuals varied between the two extremes of being formed almost entirely of acini composed of one or other of the two extreme types of cell, but the two glands of the same individual resembled each other closely. The interstitial tissue of those glands composed chiefly of the columnar type of cell appeared relatively more scanty than in those composed chiefly of the cubical. The lumina of the acini composed of the columnar cells were usually smaller than in those composed of cubical or flattened cells. From the facts that all gradations between the two extreme types of cell occurred, and that glands were seen consisting almost entirely of one extreme type or the other, it seemed probable that the various appearances seen in the epithilial cells represented various stages in the activity of a single kind of cell, and not different kinds of cells.

The smaller ducts were lined by a layer of columnar epithilium resting on a layer of cubical cells, the cells next the lumen not infrequently contained mucin. The larger ducts were lined by a stratified epithilium resembling that of the vagina.
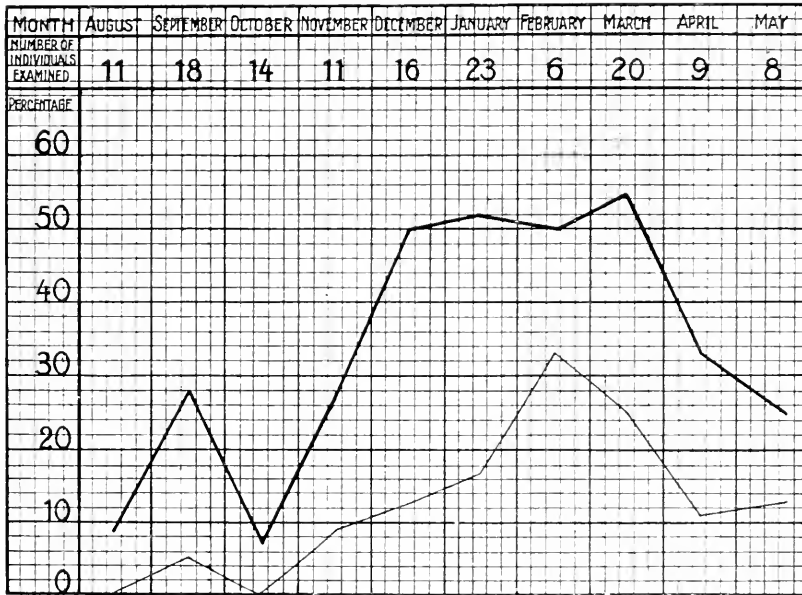
Secretion in the acini appeared in two forms: (i) as a network

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giving the reactions of mucin and (ii) as a homogeneous, gelatinous looking mass, which did not give the reactions of mucin, but retained the iron haematoxylin stain with some tenacity. These two substances were quite distinct, no intermediate stages between them ever occurred though mixtures of the two in the same acinus were frequently seen. Those acini formed of the columnar mucinous cells most frequently contained mucin, while the homogeneous substance was usually seen in dilated acini formed of short cells with little or no mucin. In a few instances, however, mucinous secretion occurred in acini whose sections showed no cells giving a mucin reaction, and conversely homogeneous secretion occurred acini the sections of which showed all the cells giving a mucin reaction. When, as commonly occurred, both kinds of secretion were found in the same lumen, the homogeneous kind usually formed a mass in the centre, and surrounding this and next the cells was a layer of the mucinous network, sometimes small islets of mucin were seen in the homogeneous mass, and lastly, where a large amount of mucin was present in the acini, islets of the homogeneous substance were present in the mucinous network. Both kinds of secretion were seen in the ducts, but when these were greatly distended, it was always either with mucin alone, or a mixture of the two containing large proportions of mucin; from this it may be inferred that when the gland is normally secreting fast the secretion leaving it is chiefly mucin. The cells of such rapidly secreting glands nearly all contained a certain amount of mucin, so from this fact it is impossible to say, whether the homogeneous secretion is secreted by the cells when they are in a more or less nonmucinous state, or whether it is due to a chemical alteration in the mucin after secretion, which takes some time to occur.

In addition to these two forms of secretion, desquammated cells were occasionally seen in the ducts and more rarely in the acini.

A considerable number of glands taken from cats which were neither pregnant nor lactating were examined, pregnancy being assumed absent when there were no localised swellings of the uterine cornua. It was found that they varied very greatly in the amount of mucin they contained in their cells. They could be roughly divided into two classes, (i) those in which about half or more of the cells seen

in a more or less equatorial section, gave a mucin reaction („mucin glands") and (ii) those in which less than half gave this reaction („non-mucin glands"). Among the „Mucin glands" were some, forming a very definite group, which consisted almost entirely of acini formed of the most extreme tall, columnar, mucinous type of cell. Individuals with „mucin glands" were usually less numerous than those with „non-mucin glands" but their proportion varied considerably with the time

MONTH	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY
NUMBER OF INDIVIDUALS EXAMINED	11	18	14	11	16	23	6	20	9	8

Curves showing the monthly incidence of Bartholins glands rich in mucin in cats which are not pregnant or lactating. Upper curve represents the percentage of cats, more than half of whose gland cells contain mucin: the lower the percentage of those with the glands formed almost entirely of tall mucinous cells.

of the year as shown in the curve, attaining a maximum from December to March in the months tried. As the signs of oestrus in a living cat appeared to be slight, the uterus and ovaries were examined in a hundred cats which were neither pregnant nor lactating, as well as the glands. Fifty-nine of the hundred had „non-mucin glands" and forty-one „mucin glands": of these latter fifteen were of the very extreme mucin type already alluded to. Corpora lutea in the ovaries were present with

approximately equal frequency in the two groups. In the cat, the Graafian follicles are at times found in an extreme state of dilatation, forming very marked projections from the surface of the ovary: this occurred in fifteen of the hundred cases, and thirteen of these or, 87%, were cats with „mucin glands", six having the extreme mucin type of gland. The uteri were divided into groups according to the development of their glands: in those with the greatest glandular development, the glands were composed of tall columnar cells, were closely packed and extended quite down to the muscle layer, at any rate in part of the circumference of the mucous membrane. Twelve of the hundred belonged to this class, eleven, or 92%, were cats with „mucin glands" and of them, eight were of the extreme mucin type. Pigment is said to occur in the uterus of the bitch most frequently in the period of recuperation of the oestrus cycle [7], this apparently has not been proved for the cat. It did occur in forty-six out of the hundred uteri examined, of these eleven, or 24%, were cats with „mucin glands". It was therefore evident that cats, whose Bartholin's glands contained large quantities of mucin in their epithelial cells more frequently had dilated Graafian follicles and hypertrophied uterine glands than average cats and less frequently had pigment in the uterus: this was more marked still for the dilated follicles and hypertrophied uterine glands if only those cats whose glands were of the very extreme mucin type were considered. These three facts seem only explicable on the assumption that the gland cells become rich in mucin shortly before oestrus and lose it at or, soon after, that time. One cat was apparently killed during oestrus or in the earliest stages of pregnancy. It had blood on the vulva, the uterus was large with a thick mucous membrane and greatly hypertrophied glands, the ovaries had no dilated follicles but corpora lutea which appeared of recent formation: in this cat the Bartholin's glands were composed entirely of cells containing mucin, none were very tall, some were short and the lumina of the acini were dilated with mucin. This gland had therefore, the appearance of one of the extreme mucin type which had begun to secrete actively.

2. Bartholin's Glands in pregnancy and lactation.

Observations on this were also confined entirely to the glands of cats. The actual duration of pregnancy was not known in any case, so the foetuses were weighed, and the duration estimated from the weights. The foetuses of a cat which had been isolated 20 days averaged 0.5 grams; in two other cats an abdominal section showed the uterine cornua to be free from external enlargements both were kept isolated, one aborted foetuses averaging 1.2 grams 20 days later and the other when killed 9 days later was pregnant with foetuses weighing 0.005 grams. From these facts it seems probable that external enlargements of the uterine cornua do not appear for several days, probably between one and two weeks, after pregnancy has commenced, and that pregnant cats with foetuses weighing one and a half grams or less, are in the first half of pregnancy. The gestation period of a cat has been assumed to be nine weeks [7]. The weight of a new born kitten varies considerably but appeared to average about 100 grams. Involution of the uterus appeared practically complete in two weeks, but the swellings of the placental sites were still just visible.

The glands of twenty-eight individuals were examined in the first half of pregnancy i. e. when the foetus weighed 1.5 grams or less, and of sixteen in the latter half. Considering the former first, the eight earliest had uterine swellings which were just visible and the foetuses were too small to take out and weigh: — less than 0.005 grams — these were probably in the first two weeks of pregnancy. Bartholin's glands in these eight cats were composed of acini of cubical or short columnar cells, a large proportion of which showed some mucin, but the amount was not great in any but two of the eight, and these had a very few cells containing a large amount of mucin: it often consisted only of a faint streak on the surface of the cell next the lumen. The nuclei were large and clear. In the four latest — foetuses $\frac{1}{2}$ – $1\frac{1}{2}$ grams, there was a much greater amount of mucin present in the gland cells. partly through a greater proportion of cells containing it, but chiefly through the presence of a considerable number of tall columnar cells containing a large amount of mucin and having deeply stained compressed nuclei: the acini formed of these cells were chiefly at the peri-

phery of the gland. Of the sixteen remaining out of the twenty-eight early pregnant cats, three had more mucin in their cells than the four glands just described, otherwise as regards their gland cells they fell into an intermediate position between the eight at the beginning and the four at the end of this period. The secretion in the ducts and acini in the twenty-eight early pregnant cases was usually a mixture of both mucin and the homogeneous substance with a preponderance of the former in only one case was a large amount present when it was largely mucin: in many cases the amount was very small.

The glands of the sixteen cats killed in the latter half of pregnancy with one exception were composed almost entirely of cells containing mucin. The exceptional case was that of a cat in which one hypogastric nerve had been stimulated in its continuity for several hours, being ligatured, but not divided, centrally to the electrode: the glands on both sides had the appearances of almost complete exhaustion: this case was most probably not a real exception but due to the technical error of not cutting as well as tying the nerve. In the remaining fifteen, a marked degree of mucin reaction was present in nearly all the cells, and in all but one, a large proportion of tall columnar cells occured, the majority of cells being of this type in most cases. The lumina of the acini and ducts contained mucin: this was never great in amount: in some cases a small number of acini were present distended with homogeneous secretion, these were usually formed of short cells.

The glands of thirteen cats were examined after parturition, before the uterus was completely involuted. In two of these the glands were obtained within twenty-four hours of parturition, in another on the fourth day after, and in two others, from the appearance of the uterus, at intermediate times. In these five cases, the glands appeared almost identical with those in the latter half of pregnancy, but the acini contained rather more mucin. Three cases whose periods were not actually known, but which were probably in the latter half of the first week, from the appearances of the uteri, had very similar glands; in two of them the number of tall columnar cells was diminished. In three, two seven and one eight days after parturition, there was very obviously less mucin in the cells: tall columnar cells were few in number and a con-

siderable number of acini contained masses of homogeneous secretion. In the remaining two the uterus was almost completely involuted, in one the mucin was still less evident, the other showed a considerable amount though all the cells were short; this last was the only case in the thirteen in which lactation was not present when the animal was killed.

The glands of twenty-one cats were examined during lactation but after involution of the uterus. Lactation was profuse in twenty of these, in the other it was only slight; in the glands of that one most of the cells contained mucin and there were a fair proportion of tall columnar cells. In one which parturition was known to have occurred two weeks before, the gland resembled those described in the second week after parturition. In another where parturition occurred a month previously the gland consisted almost entirely of dilated acini formed of short cells rather less than half of which contained mucin, the acini contained both mucin and homogeneous substance. Later, two and a half months after parturition, a case showed the gland to be formed of acini of flattened cells, hardly any of which contained mucin, and a large number the acini were distended with homogeneous secretion; mucin was absent from the lumina of the acini. With four exceptions the glands of the twenty cats in which lactation was profuse, fell more or less into a series with the two weeks and the two and a half months glands at its extremes: most of them approximated more to the two and a half months. The exceptional cases all showed glands with a very large amount of mucin in their cells. The uteri and ovaries of each animal were examined as in the non-pregnant ones. The ovaries of three of the twenty-one lactating cats had marked dilatation of the Graafian follicles and these all occurred in the four exceptional cases; the uterine glands showed a considerable hypertrophy in five cases and four of them were the four exceptional ones. It was thus clear that a large amount of mucin occurring in the cells of Bartholin's glands during lactation was exceptional, and when it occurred, was associated with the same uterine and ovarian conditions as when it occurred apart from pregnancy at all. It was therefore due probably to the onset of oestrus during lactation. The case with very little milk did not come

into this group and no explanation of the mucin in its cells could be given.

It is therefore evident, that in cats, during the first half of pregnancy, the epithelial cells of Bartholin's glands become rich in mucin: this reaches a maximum early in the second half and then remains stationary till a few days after parturition when it begins to decrease fairly rapidly, first at the expense of the amount of mucin in each individual cell, and later, by the cells containing mucin becoming fewer, finally, in the late stages of lactation, all the cells are short or flattened and hardly any contain mucin: this change in the appearance of the cell is accompanied by a change in the secretion seen in the lumina, from mucin to the homogeneous substance. Exceptionally oestrus may occur during lactation, and then it is accompanied by the change in the gland cells already described. These facts suggest that during pregnancy the glands prepare themselves for some unusual secretory effort, which begins at, or soon after, parturition and lasts approximately while the uterus is involuting, they then settle down into a resting condition. If, as occurs in the mare, oestrus in the cat took place a few days after pregnancy, the condition of the glands at parturition could be easily explained. That it does not, at any rate when the kittens are allowed to live, is shown by the fact that cats do not usually litter at intervals of two and a half months. The change in Bartholin's glands must therefore be a true phenomenon of pregnancy and not of oestrus occurring shortly after parturition. Further, though the glands in both instances are rich in mucin, there are slight histological differences: the glands of late pregnancy never being quite as completely formed of the tall columnar cells as are those of oestrus. In the four cases mentioned where a large amount of mucin was present in the gland although lactation was profuse, the period was only known in one, in which it was between six and seven weeks after parturition. The very marked mucinous type of gland was also found in one cat, about three weeks after parturition, when the kittens had been taken away and lactation had ceased.

3. Variations in Cowper's glands.

Stilling [10] described changes in the Cowper's glands of rabbits after coitus without any special reference to mucin, which is only present in small quantities in the glands of that animal.

The glands of cats, rats and guinea-pigs were examined in animals which had been isolated for considerable periods and in those which had had every chance of performing coitus, though in no case was this known to have taken place shortly before the animal was killed. No differences were found in the two classes. The Cowper's gland of the cat appeared to vary very much less with regard to the mucin it contains than the Bartholin's gland, and further, what it does contain is much more evenly distributed. In the rat and guinea-pig the individual variations and unevenness of distribution in the mucin are much less still than in the male cat.

II. Influence of nerves.

The nerves sending branches to the bulbo-urethral glands or their vicinity are the pudic, the pelvic visceral and the hypogastric. To determine the effect of stimulation of any of these nerves on the glands, the nerve was divided and a protected electrode put on its peripheral end. In a few cases the nerve was ligatured without division, but this method is unsatisfactory. The stimulus used was the secondary current of an induction coil, of such an intensity as to be easily felt on the tongue but not painful; in exhaustion experiments, the stimulus was gradually increased in strength by approximating the secondary to the primary coil. Ether was used as the anaesthetic in most cases, in the remainder chloroform. In most exhaustion experiments on cats, the animal was pithed, the anaesthetic discontinued and artificial respiration performed after all operative manipulations had been completed. The pudic nerve was approached through a vertical incision just internal to the ischial tuberosity and the pelvic visceral through an oblique incision in the iliac region parallel to Poupart's ligament; in cats this operation was extraperitoneal, in guinea-pigs the peritoneum was opened and divided again where it is reflected off the prostate on to the side of the pelvis. In

guinea-pigs, rats and survival operations on cats access to the hypogastric was obtained intraperitoneally, through a median abdominal incision: in other experiments on cats extraperitoneally, through a lumbar incision: it was divided at, or close to, the inferior mesenteric ganglion and stimulated just peripherally to the division.

The orifices of Bartholin's glands in the cat can be easily seen if the perinaeum is divided mesially in a dorsal direction. The presence and rate of secretion escaping from the duct was estimated by periodically touching the orifice with the corner of a small piece of blotting paper. By this means it was seen that stimulation of the pudic nerve produced instantaneously a flow of secretion from the orifice of the same side simultaneously with the contraction of the perinaeal muscles: this flow ceased almost at once, whether the stimulus was continued or not: after cessation of the stimulus a slight flow in some cases began again. The effect of stimulating the pelvic or hypogastric nerves was quite different to that of the pudic: after a variable latent period of from seven to fifty seconds, a flow of secretion from the orifice commenced, this lasted as long as the stimulus — at any rate up to ten minutes — and continued for some seconds after the cessation of the latter. The variation seen in the latent period seemed to depend on variations in the amount of ducts of the gland were already distended, it was longer the first time the nerve was stimulated than subsequent times, and was increased again if the pudic nerve of the same side was divided: therefore, the shortest time observed is probably about the true latent period of secretion. This effect of stimulating the hypogastric could not be obtained if the inferior splanchnic nerves had previously been divided where they enter the inferior mesenteric ganglion and allowed to degenerate, showing these secretory fibres of the hypogastric do not arise in the cells of the ganglion but pass through it: stimulation of the pelvic still caused secretion after degenerative section of the inferior splanchnics. The intravenous injection of 40 milligrams of nicotine completely abolished the secretory effect of both nerves on the gland. It appears, therefore, that while the hypogastric and pelvic nerves contain secretory fibres to Bartholin's gland, the pudic only supplies the capsule of striped muscle and contains no secretory fibres, and

further that ganglia are situated peripherally in the course of these two secretory nerves. The effect of stimulating the pelvic nerve was not quite as constantly obtained as that of the hypogastric, but that it is a true effect of the pelvic itself, and not due to an accidental stimulation of the peripheral part of the hypogastric, was shown by the fact that it could be obtained when the divided nerve was held quite out of the wound and stimulated against the ligature. No direct observations of this nature were made on Cowper's glands, attemps in the cat and guinea-pig were always frustrated by haemorrhage obscuring any secretion that might have occurred.

For the purpose of exhausting the glands, the nerve of one side was usually stimulated for seven minutes and rested three in every ten, and the gland of the other side used as the control. The duration of stimulation necessary to produce marked histological changes varied both in different species and in different experiments on the same species. In cats five and a half hours stimulation was usually aimed at, making the duration of the experiment eight hours, though marked effects were seen in some cases after three hours stimulation, or even less. In the case of the cat's Bartholin's gland, prolonged stimulation of the pudic nerve produced no changes in the cells of the gland that could be seen but the amount of secretion in the acini and ducts on the stimulated side was less than on the control. After prolonged stimulation of the pelvic visceral nerve also, the acini of the gland on the same side were usually more contracted and contained less secretion than those of the opposite side. In only one instance out of seven in which the pelvic nerve was stimulated for three hours or longer was there any appreciable diminution in the amount of mucin in the gland cells themselves: in this case the diminution was slight and nothing approaching that seen after stimulating the hypogastric for the same length of time, though it was probably too great for an accidental pre-existing difference: it might have been due to faulty insulation and a leak of current to the peripheral part of the hypogastric. Prolonged stimulation of the hypogastric produced a disappearance of mucin from the cells, which was more or less complete according to the length of time the nerve was stimulated: the acini in such cases were either empty

or had a thin layer of mucin adhering to the free ends of the cells. The contrast with the control gland was best seen when this was rich in mucin, as in late pregnancy or the early puerperium. Exhaustion appeared to occur with equal facility in either of these two cases though, as previously shown, they are in different phases of activity. In such a case the tall, columnar cell with a compressed, deeply stained nucleus at the base, giving a marked reaction with mucin stains, became much shorter or even cubical, with a clear, round nucleus having a well marked nucleolus and chromatin network, and gave no reaction with mucin stains. The cell protoplasm on the exhausted side stained rather more deeply with iron haematoxylin, whereas on the normal side this hardly stained at all; hence with this stain alone, the separation between adjacent cells was more obvious on the normal side; but when both where stained with muci-carmine in addition, this stain more or less obscured the boundaries on the normal side but left the exhausted cells unaffected, so then the separation was more obvious on the stimulated side. When small quantities of mucin remained in the cells of the stimulated side, it usually occured at their free ends near the lumen. A gland exhausted in this way differed from one normally containing minimal quantities of mucin, e. g. in lactation, in having larger cells, all the acini contracted and none of the homogeneous kind of secretion in any of the acini. These effects could not be produced in cats whose inferior splanchnic nerves had been divided at their entrance into the inferior mesenteric ganglion six to eleven days previously. In one experiment the hypogastric was stimulated for five and a half hours and nicotine injected intravenously at intervals, no exhaustion was produced. This method however was not satisfactory, as after the first fifteen minutes, it was found impossible to completely abolish the cervical sympathetic effect on the pupil, by which the injections were controlled, even with very large doses, and further, the enormous quantity of nicotine necessary to keep this effect minimal — over 0,75 grams were given in the eight hours — produced a general condition which it seemed probable, would militate against the free secretion of a gland wherever the ganglia of its nerves were situated. These facts show that while both hypogastric and pelvic visceral nerves con-

tain secretory fibres for Bartholin'a gland, the hypogastric has a very marked effect on the excretion of mucin from the cells, whereas the pelvic has at most very little, and probably none at all.

The glands showed no histological changes a week or more after division of one pelvic or hypogastric nerve. Cowper's gland in the cat appeared to have the same nerve supply as Bartholin's though secretory fibres to it in the pelvic nerve have not been demonstrated. Prolonged stimulation of the hypogastric produced a marked diminution in the mucin of the gland cells on the same side: for some reason complete exhaustion of the cells appeared more difficult to obtain than in the female. This effect was abolished by previously dividing the inferior splanchnic nerves and allowing them to degenerate. Prolonged stimulation of the pelvic or pudic nerves produced no alteration in the gland cells at all.

Marked diminution in the mucin of the cells of Cowper's gland was produced by stimulation of the hypogastric nerve in the guinea-pig and the rat. One and a half hours stimulation in the case of the guinea-pig usually produced an obvious effect and in the rat an even shorter time: the experiments were more difficult than in the cat owing to the much greater difficulty of keeping the animal alive under an anaesthetic for a sufficiently long period. The effect in the guinea-pig was abolished by degenerative section of the inferior splanchnics: in the rat this experiment was not performed.

Prolonged stimulation of the pelvic nerve in the guinea-pig produced no changes in the gland epithilium, this was not done in the rat. Division of one hypogastric or pelvic nerve produced no histological changes in the corresponding gland in guinea-pigs nine and twelve days after the operation respectively or in a longer period; this was the same whether the animals were isolated or in cages with females.

III. Effects of removal of the testes or ovaries.

It was first observed by John Hunter that the Cowper's glands of animals castrated when young failed to develop at puberty, and subsequently by Griffiths [4] that in the cat they underwent regression after castration in adult life. This regression is best seen in such ani-

mals as the guinea-pig where the muscular capsule is not very thick, as in the cat, nor the gland complicated by a large dilated duct as in the rat. It was found that the glands of five guinea-pigs, varying from 550 grams to 810 grams, and castrated in adult life $5\frac{1}{2}$, 6, 6, 7, and 10 months previously, weighed respectively .054, .075, .121, .075 and .095 grams: while twenty-five normal guinea-pigs varying from 400 to 765 and averaging 517 grams had Cowper's glands weighing from .102 to .255 grams and averaging .161. The effect of castration on the mucin was found to vary in different animals. In the guinea-pig there was hardly any effect at all when the adult was castrated, the mucin reaction both of the cells themselves and of the secretion in the lumina of the ducts and acini was quite as marked as in the intact animal: the only obvious histological difference was that the lobes of the glands were separated from each other by a greater thickness of interstitial tissue and muscle, the individual gland cells were rather smaller and the nuclei on the whole not so compressed or deeply staining: the two last differences were very slight. If the animal was castrated when young e. g. five weeks old, the same differences occurred but were much more marked, the gland resembling that of an animal of the age at which it was castrated, and like the latter showing a well marked mucin reaction in each individual cell.

In the rat castration in the adult produced a more marked effect on the Cowper's glands than in the guinea-pig in three to four months the acini became much fewer and the cells much smaller but both they and the secretion in the duct still gave a mucin reaction. The glands of the water vole (Arvicola amphibius) in autumn were found to normally have taken on an appearance very like those of the rat some months after castration.

In the cat no animal was castrated for the purpose of seeing the effect on Cowper's glands but the glands of a considerable number which had been castrated at an unknown date were examined. The glands were all small. The pad of fat that normally exists between the capsule and the gland was usually increased at the expense of the glandular tissue. Some glands gave no mucin reaction in their cells at all, most gave it slightly and a very few moderately, none at all

gave it in the marked way that is quite often seen in normal cats: the practice of castrating adult cats is so common that it is unlikely all those examined had been operated on before puberty.

Double ovariotomy was performed on five adult cats, which were kept three, six six, twelve and twelve months after respectively. In all cases Bartholin's glands were very small and in two so small as to be below the normal variations of the gland in intact cats. The glandular epithilium consisted entirely of cubical or flattened cells, mucin only occurred in a very few of them and in some sections no cells containing it could be seen: acini dilated with homogeneous secretion were frequent, in some no mucin was present in the acini, in others a faint streak of it between the cells and the homogeneous secretion. In two cats one ovary only was removed, these were kept three and six months after the operation: in both, the remaining ovary had dilated follicles when they were killed and the Bartholin's glands, which resembled each other in size and structure, were formed of cells of the tall columnar type normally associated with this condition of the ovaries. In two cats the ovaries were removed within twenty-four hours of parturition: they continued suckling and were killed respectively two weeks and a month after, the Bartholin's glands in both cases showed considerably less mucin in the cells than those of control cats of the same period in which double ovariotomy had not been done: probably a larger number of experiments on this last point would be necessary to eliminate individual variations.

Removal of both ovaries therefore, prevents the development of a large amount of mucin in the cells of Bartholin's glands and, as far as experiments have gone, accelerates its disappearance when already present. Removal of one ovary, as would be expected, has no effect on the glands.

IV. Functions of the glands.

Numerous suggestions have been made as to the functions of Cowper's glands, all, with one exception unsupported by experimental evidence. The single exception is the observation of Camus and Gley [2] that the secretion of Cowper's gland in the hedgehog — which

they call the external prostate — causes coagulation of the secretion
of the vesicular seminales: that in the guinea-pig and rat this action
was brought about by the secretion of the prostate was shown by
these observers themselves [1], and it has since been shown by Walker
[12] that it is only brought about by the secretion of a special small
part of the prostate, which he has termed the coagulating gland. This
fact, therefore, throws no light on the function of the glands in rats
and guinea-pigs, in animals which possess no vesiculae seminales or
in those in which a „bouchon vaginal" is not formed. Further, the ho-
mology of the Cowper's gland of the hedgehog appears to be open to
question [3 and 9].

To determine whether the glands played any part in the breeding
powers, they were removed from ten rats and ten guinea-pigs. In all
cases the animals were known to have bred before the operation, and
in all the complete removal of the glands was confirmed post-mortem.
At varying periods after the operation they were mated with two or
three females, some or all of which were known to have bred previously.
In the case of the ten rats, five bred at periods from nine days to eight
weeks after the operation, all five were mated a week or less after the
operation. The remaining five, which did not breed, were mated two
to thirteen days after the operation: they died or were killed nine to
thirty weeks after mating: one died from a purulent discharge from
the upper air passages to which rats appear to be subject: the other
four were all old judging from the condition of the fur, in three of them
an atrophic condition of the testes was present, in the fourth the testes
had been eaten by the females before the body was recovered, so they
could not be examined: this atrophy appeared common in old rats
and there was no reason to think it had anything to do with the ope-
ration. In the ten guinea-pigs, five bred from five to forty-eight weeks
after the operation, these had been mated seven to forty-four days
after the operation. Of the five which did not breed, one was mated
fifty-three days after the operation and died sixteen days after that:
it appeared old and had atrophic testes. One was mated in six days
and died fifty-seven days later without any cause for death being
found. Three, which were mated in four to thirteen days, died from

twelve to nineteen later: these probably all died from an incomplete
— at any rate anatomically — lesion of one or both pudic nerves
which are in close association with the glands in guinea-pigs: one of
these had a plug of vesicular secretion in the posterior urethra with
the urethra behind it, the bladder and both ureters dilated: the other
two both had vesicular secretion in the bladder or urethra, which ap-
peared to have been there before death, but there was no evidence
of urinary obstruction: in these two, one or both perinaeal folds were
flaccid, indicating an injury to the pudic: this was not looked for in
the first of the three. It is therefore certain, in these animals Cowper's
glands are not necessary for the performance of fertile coitus and pro-
bable, that their removal has no influence on it: in both cases five out
of six is a fairer proportion of the animals that bred than five out of
ten, since four rats and one guinea-pig appeared too old to breed and
three guinea-pigs died as an indirect result of the operation. In no case
did any compensatory hypertrophy of the prostate or vesiculae semi-
nales occur.

Conclusions.

(i) The glandular epithilium of Bartholin's glands in cats becomes
rich mucin in shortly before oestrus and in the last half of pregnancy.

(ii) Secretory fibres to this gland are contained in both the hypo-
gastric and pelvic visceral nerves, but not in the pudic. The ganglia
are situated peripherally in both cases. The hypogastric alone con-
trols the secretion of mucin. Cowper's glands are probably innervated
in the same way: the hypogastric certainly has the same influence:
this applies also to the glands of the guinea-pig and rat.

(iii) Castration in adult life in the guinea-pig has only a very slight
effect in diminishing the mucin content of each individual cell, in the
rat this is fairly marked though the cells still contain mucin, while in
the cat it is probably much more marked still.

(iv) Double ovariotomy in adult cats produces a diminution in
the size of Bartholin's gland and an almost complete abolition of mucin
in the cells.

(v) Removal of Cowper's glands in rats and guinea-pigs has no
effect on their breeding powers.

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Plates.

I and II. The right and left Cowper's glands of a guinea-pig. The left hypogastric nerve had been divided and its peripheral end stimulated for $1\frac{1}{4}$ hours.

III and IV. The right and left Bartholin's glands of a pregnant cat, the foetuses averaged 50 grams each, the left hypogastric nerve had been divided and its peripheral end stimulated $5\frac{1}{2}$ hours.

V. The Bartholin's gland of a lactating cat in the tenth week after parturition.

The glands were fixed in a sublimate-formol-acetic mixture, sections cut in paraffin and stained with Mallory's iron haematoxylin and muci-carmine.
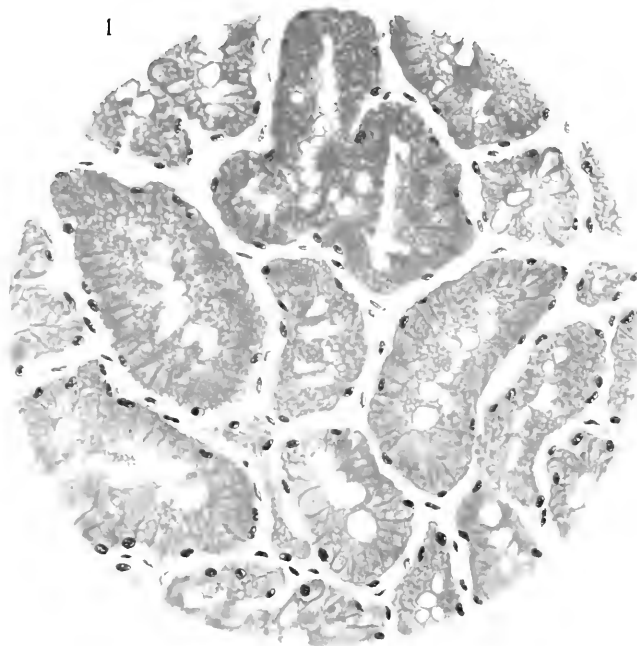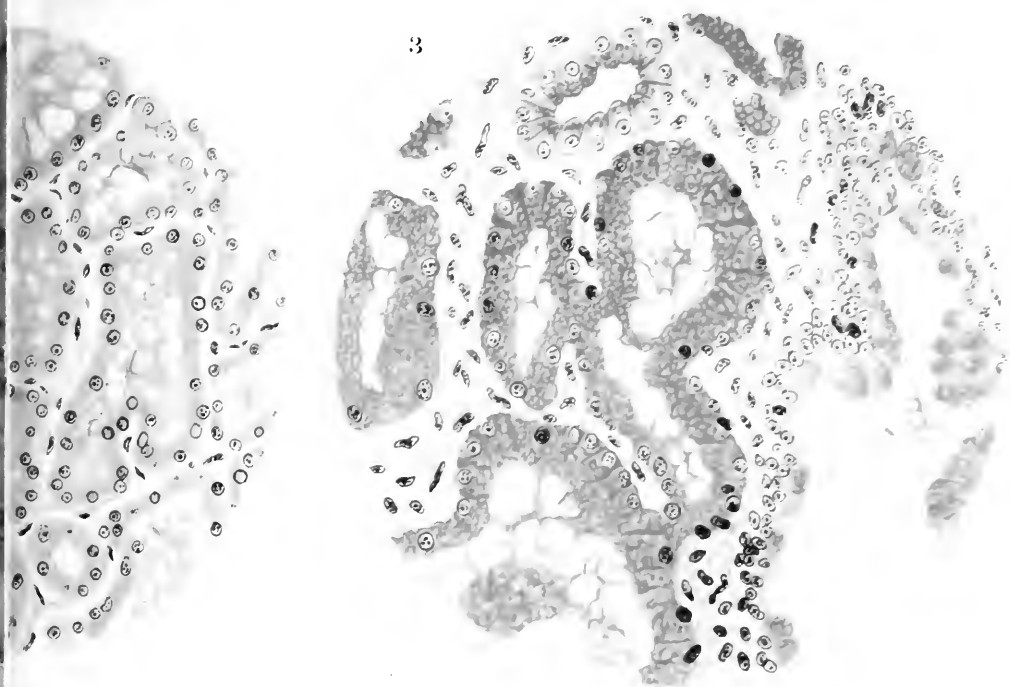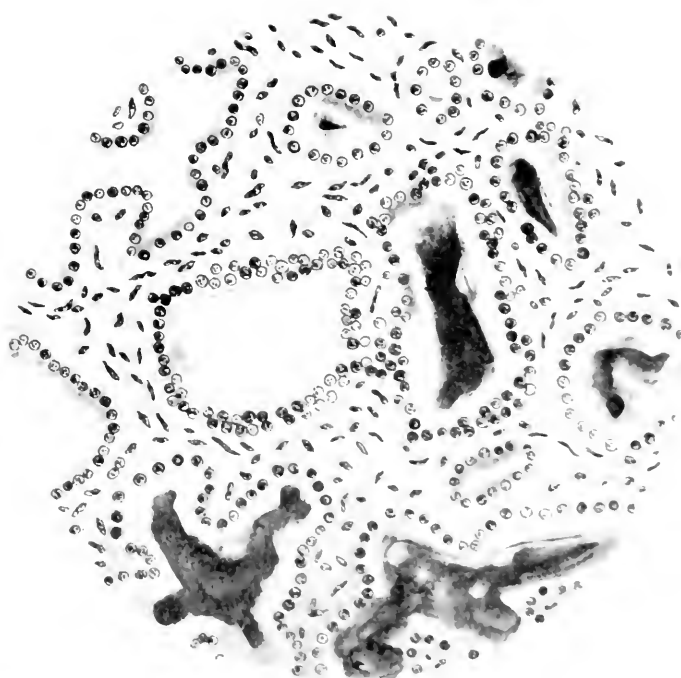
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WILFRED TROTTER (University College Hospital, London) and **H. MORRISTON DAVIES** (University College Hospital, London).   The peculiarities of sensibility founds in cutaneous areas supplied by regenerating nerves.

(From the Research Laboratories of University College Hospital Medical School, London.)

With 6 Figures.

Contents Table.

Introduction.

The processes whereby a peripheral nerve which has been divided regains its normal activity are of great interest to the physiologist as well as to the clinician and have been extensively studied by both. In so far as motor nerves are concerned the physiologist has been able to deal with the subject in both its principal aspects namely the histological phenomena of the anatomical restoration of the nerves and the phenomena of the recovery of function. In a general way the results thus obtained agree with those observed by the clinician in the human subject, allowance being made for the fact that in the latter case the recovery is from lesions made accidentally and not under experimental conditions.

In regard to sensory nerves however the case is different. Here the investigations of the physiologist are almost necessarily limited to histological observations and he has not been able to make by animal experiments exact enquiry into the recovery of function.

It was for a long time assumed that the recovery of sensory function was a gradual and uneventful restoration to the normal corresponding with the histological events of regeneration, possibly varying in length in different cases but tending always in time to be complete. The area of skin deprived of sensibility by the nerve section would thus shew during recovery no form of sensibility which

could not be described as a hypoaesthesia. It would be stating the case very modera-elty to say that such an orderly progress of events was unfamiliar to the clinician. Many unaccountable peculiarities of sensibility were from time to time observed to occur but as they were not explained or even described by the physiologist and were phenomena particularly insusceptible to exact description by the clinician they tended to be regarded as in some way accidental and not essential accompani-ments of the functioning of the sensory nerve during recovery.

In 1905 an important contribution to the subject was published by *Henry Head*. He had made the great step in advance of applying the methods of experi-mental physiology to the investigation of the problem in the human subject and had submitted to the production of an area of anaesthesia in his own forearm and hand by the section of the cutaneous nerves supplying it. The nerves had been sutured and the ensuing phenomena closely observed and these phenomena studied for the first time under experimental conditions were found to be capable of exact and detailed description. Many of them were of a remarkable and unexpected character and the whole body of observations was used as the foundation for a hypothesis concerning the intimate physiology of the peripheral nervous system even more striking than the facts upon which it was based.

Both the facts and the hypothesis of *Head* were striking enough to make it clear their full value could scarcely be appreciated until they had been confirmed by investigations in which the same method was used by other observers and it was with this object in view that in 1907 we began a series of experimental nerve sections upon our own cutaneous nerves. In this investigation our guiding prin-ciple was that nerves should be cut in both of us at different times so that the material on which our conclusions were to be based should be drawn from as wide a field as possible and also so that the knowledge gained in investigating the phenomena of one experiment could be used to amplify and coordinate our methods in the next.

In this communication we propose first to describe and examine the facts of the recovery of function after section of a sensory nerve comparing our observations with those of *Head* and attempting to indicate those which we regard as definitely established. Secondly to discuss the various hypotheses which have been advanced in explanation of any or all of these facts. And thirdly to put forward certain views of our own which our investigations have led us to entertain.

Phenomena of Recovery.

a) *Material on which observations are founded.*

It will be convenient to begin with a summary account of our own personal observations. The material for these was obtained by the division in one or the other of us of the following nerves: Internal saphenous, Great auricular, Internal cutaneous of arm (nervus cutaneus brachii medialis), a branch of the middle cutaneous of thigh.[1] In the case of the internal cutaneous the whole area of distribution of the nerve was rendered anaesthetic by dividing its three branches at three separate operations. In order that the basis of enquiry might be as broad as possible we

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[1] In every case a piece of the nerve trunk from 5 to 10 mm in length was excised and the ends united by sutures.

chose nerves in widely different parts of the body and of very different sizes varying
from such as supplied small areas, to nerves like the internal saphenous and the
internal cutaneous, the section of which produced areas of anaesthesia of 280 sq. c. m.
and 122 sq. c. m. respectively. To obtain material for very exact comparison of
results in two different individuals, a branch of the middle cutaneous of the thigh
in each of us was divided. These precautions made the research very prolonged
but justified themselves in the extent and diversity of the experience they gave us.

To such as may be disposed to prosecute researches in this department of
physiology we would take this opportunity of remarking that proportionally to
the interest of the work the amount of inconvenience incident upon having a cuta-
neous nerve or two divided is extremely small. It would be easy for anyone without
actual experience to overestimate the discomforts of these small essays in experi-
mental physiology. The largest nerve we cut was the internal saphenous at the
knee and the section rendered anaesthetic nearly the whole of the inner aspect
of the leg. Yet the subject of the operation has experienced from the lesion nothing
but the most inconsiderable discomfort at any time. It is true for reasons we shall
have to refer to in the concluding section of this paper, that a certain degree of
temperamental stability is desirable in the subject of such an interference but this
is of course also necessary for the general work of the observations if results capable
of reliance are to be obtained.

b) *First Appearances of Recovery.*

We do not propose to enter upon the description of the alterations of sensibility
produced by the nerve section: this has been dealt with fully in our earlier paper.[1]
It may however be stated that each area of sensory defect shewed for some weeks
previous to the first appearance of recovery a well defined, stable and stationary con-
dition. In the central part of the area there was profound loss of cutaneous sensi-
bility of all kinds and surrounding this was a fringe of varying width which shewed
a hypoaesthesia to all forms of stimulation; this hypoaesthesia being most intense
towards the central part of the area and diminishing gradually away from it. We
wish to lay particular stress upon the fact that in this quiet period immediately
preceding the first appearance of recovery we never observed any phenomena
except those of reduced sensibility and it frequently happened that the possessor
of such an area of sensory loss was quite unconscious of its presence in the intervals
between examinations. As soon however as recovery began the subject became
more or less continually aware of the abnormal region of his skin.

The first clear evidences of the beginning of the restoration of function were
usually to be observed between the 10th and 12th weeks after the nerve section.
Thermal sensibility, tactile sensibility and sensibility to pain began to reappear
in all cases about the same time; and it is interesting to notice that the motor func-
tions of the cutaneous nerves (pilomotor, sudomotor) shewed signs of beginning
restoration at about the same period. In every case the reappearance of function
occurred first in the proximal part of the affected area at and about the spot where
the nerve entered it. Beginning thus the evidences of recovery spread gradually

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[1] "Experimental Studies in the Innervation of the Skin". Journal of Physiology. Vol. 38
Nos. 2 and 3. 1909.

towards the distal extremity of the area. The time taken for complete restoration to the normal was at least many months and usually more than a year. In regard to this matter however it is very important that a clear distinction should be made between restoration of sensory acuity and restoration of the normal quality of sensation. The former, when it occurs is always much more rapidly completed than the latter, and it is to the former that the periods specified above refer.

Sensibility to all forms of stimuli is, as is well known, distributed in the skin in minute areas or spots and when a region is recovering sensibility as a result of regeneration of its nerve the reappearing function is localised in isolated spots also.

It would seem to be very generally taken for granted that when the ends of a nerve have been stitched together, and the wound has healed without suppuration, complete recovery of function is merely a question of time. The process of recovery may in fact however be arrested at any stage and a permanent defect of sensibility remain.

c) *Return of Sensibility to Touch.*

The sensation elicited by tactile stimuli is to the trained observer one of the most definite and characteristic which he can experience. It possesses qualities which mark it off from all other sensations as clearly as is marked off the sensation of cold or that of pain. *von Frey* has shewn that the peripheral mechanism of this form of sensibility is intimately associated with the hair bulbs, that the movement of the hair bulb is essential to the production of the sensation and that therefore the stimulus which calls forth the sensation must be an actual movement at the moment the sensation is produced. In other words when the skin is touched a tactile stimulus is given at the moment when contact is made and at the moment when contact is broken but not in the interval if the stimulating object is kept in motionless contact with the skin. The best method of investigating this form of sensibility is the well known hair aesthesiometer of *von Frey* which enables exact quantitative estimations to be made. Examination of an area in the quiet period before the appearance of recovery will shew a central region in which the characteristic tactile sensation cannot be elicited with any of the *von Frey* hairs, however strong; surrounding this and between it and the normally sensible skin is a relatively narrow zone in which the sensation of touch can be elicited but only with hairs stronger than those necessary to stimulate normal touch spots.

It will be found about 10 to 14 weeks after the nerve section that this hypo-aesthetic zone begins to increase at the expense of the anaesthetic area in the region where the nerve trunk enters it. That is to say a few spots will be found in this region, where at former examinations no touch sensation could be elicited which now yield that sensation but only when stimulated by hairs giving a stimulus well above the normal threshold of the part. It is clear therefore that although sensibility to touch returns thus early, it reappears in a distinctly hypoaesthetic form so that the return of it at this date might very easily be altogether overlooked if the examination for it were made by a method which involved the use of a stimulus of fixed strength such as that given by cotton wool or a camel's hair brush.

During the ensuing months the return of sensibility to touch gradually extends throughout the area from the proximal to the peripheral extremity, always

appearing first along the line of the nerve. By the 6th to the 8th month, supposing recovery to be proceeding in the normal way, touch spots, from which the characteristic sensation can be elicited will have appeared throughout the whole area though not distributed with their normal density. Most of the spots however will still be distinctly hypoaesthetic and will need a stimulus well above the normal threshold to yield tactile sensation. It is not therefore until after this period that the area begins to respond to stimulation with cotton wool. The sensibility thus regained shews certain other peculiarities than hypoaesthesia. These peculiarities concern the quality of sensation and the localisation of it. First as to quality, it may be said that while each touch felt has the characteristics of that sensation, it possesses also certain other features which the subject recognises as being altogether new but very difficult to define. The sensation has a certain sharpness in it, not recognisable in a normal touch and resembling somewhat the tingling vibration produced by the faradic current. This peculiarity is not very easily detected during the stimulation of a single touch spot with a *von Frey* hair but is very striking when a considerable area of recovering skin is stimulated at one time. With regard to localisation a very striking phenomenon is noticeable from the first moment of recovery and this is that when a recovering spot, necessarily of course at the proximal end of the area is stimulated, the corresponding sensation, instead of or in addition to being felt locally, is felt in the extreme peripheral end of the area which is still at this early stage anaesthetic: this is the phenomenon which we have called "peripheral reference". As we shall see later it is not peculiar to tactile sensations. It is one of the earliest and most characteristic accompaniments of recovery and also one of the most persistent for it may be quite definitely observable years after the area has recovered its normal sensory acuity.

d) *Return of Thermal Sensibility.*

In the period preceding the first appearance of recovery, the affected area presents a central region of thermo-anaesthesia surrounded by a zone of thermo-hypoaesthesia which gradually fades into the normal sensibility of the unaffected skin.

The study of thermal sensibility is a peculiarly difficult one not only in regard to technical detail but especially in regard to obtaining clear conceptions on the subject and expounding them without confusion. It is particularly important that a perfectly definite idea should be obtained as to what is meant by thermo-hypoaesthesia. Thermal sensibility is localised to two series of spots scattered in the skin, one series being sensitive to temperatures above, and the other sensitive to temperatures below that of the skin at the moment of testing. It seems that the peripheral mechanism whereby a thermal sensation is aroused depends upon the transference of heat to the skin or the abstraction of heat from the skin by the stimulating object, the former type of interchange always stimulating one series of thermal spots (heat spots), the latter type of interchange stimulating the other series (cold spots). When it is kept in mind that thermal sensibility registers heat transference and in no sense absolute temperature, it becomes clear that the temperature of the skin itself is of fundamental importance in determining whether stimulation by an object at a temperature at all near that of the skin will produce

a sensation of the cold series, a sensation of the heat series or no thermal sensation at all. It is common knowledge that an object may be made to feel cool or warm according to the temperature of the skin without its own temperature being altered, but it is not equally obvious that objects whose temperatures are very near that of the skin can give rise to no thermal sensation at all. There is however in fact an insensibility of the skin to temperatures ranging over about 5 degrees centigrade of the thermo-metric scale. This normal intermediate insensibility can of course be shifted upwards or downwards by warming or cooling the skin respectively. Thermal stimuli bordering on this range of intermediate temperatures give rise to sensations of very slight intensity, cool or warm in quality according as the stimulus is below or above the temperature of the skin. As the stimulus temperature departs from that of the skin, so the corresponding sensation becomes more intense, and it is generally necessary for there to be a difference of 15 degrees between the stimulating object and the skin before the maximal sensation — cold or hot — is elicited. If we now consider what would be the effect of a general reduction in the thermal sensibility of the skin it becomes obvious that this must produce an increase in the range of intermediate insensibility and a diminution in the intensity of sensations produced by the various stimulus temperatures. For example suppose on normal skin an object at 32° C to be indifferent, one of 35° C faintly warm, one of 38° C warm and one of 50° C hot. If such an area of skin becomes hypoaesthetic 32° C and 35° C will now both be indifferent. 38° C will be faintly warm and 50° C will be warm while it may not be possible to elicit the sensation "hot" by any temperature. This is the condition which we found to obtain after nerve section in the zone of thermo-hypoaesthesia surrounding the area of thermo-anaesthesia. The first sign of recovery occurs about the same time and in the same region as the reappearance of sensibility to touch. It consists in the development of a few spots in the most proximal parts of the affected area which yield sensations of cold when stimulated with a cold object. The nature of the sensibility of these spots is however peculiar in that the sensations elicited by stimulation are very intense and the phenomenon of peripheral reference is very clear. It would be impossible to exaggerate the intensity of the sensation of cold yielded by these spots whether it is felt locally or at the place of peripheral reference. As is well known the intensity of the sensation of cold produced by stimulation of normal skin varies directly with the size of the area stimulated. In order therefore to get some actual measure of the intensification of sensation in these recovering cold spots it is necessary to find by experiment how large an area of the normal skin must be stimulated to produce a sensation of equal intensity. We found that a single active cold spot in a recovering area stimulated with a metal cylinder having a contact surface 1 mm in diameter gave a sensation as intense as that produced by stimulation of normal skin with a metal disc at the same temperature as the cylinder but 25 mm in diameter, that is to say the sensation yielded by this cold spot was equivalent in bulk to that yielded by an area of normal skin 600 times as large.

Recovery progresses by the gradual spread throughout the area of reappearing cold spots accompanied by the characteristic intensification and peripheral reference. These latter phenomena are found not merely in the area previously anaesthetic but also in the zone previously hypoaesthetic.

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The reappearance of sensibility to temperatures above that of the skin is a slower process and usually lags behind that of sensibility to temperatures below that of the skin by some months. The restoration of sensibility to heat however when it does begin, occurs and proceeds in the same way, namely by isolated and slowly thickening groups of spots. In addition to the restoration of sensibility to heat being actually a slower process the delay is rendered more evident by the facts that the heat spots appear in smaller numbers and are consequently more difficult to find than the cold spots and that all testing for sensibility to temperatures above that of the skin is especially difficult.

Another mechanism contributing to this delay is probably the following. As we shall shew all other sensations during recovery display a marked and characteristic intensification. Now the fully developed normal sensation "hot" is not without a certain element of sting easily accessible to introspection. This sensation under normal circumstances is elicited by temperatures of about 50° C. With temperatures but little higher the thermal element in the sensation rapidly diminishes and the pain element rapidly increases until at about 55° C or even less we get a sensation of stinging pain which although we may suspect it from its character to be of thermal origin yet has little or no true thermal quality. If then sensibility to heat has during recovery that intensification which all other sensations shew — and there is strong reason to believe that this is the case — stimulation of the returning heat spots with temperatures which normally elicit the sensation "hot" will yield sensations of stinging pain having little or no true thermal quality. This is found in fact to be the case. At a comparatively early period of recovery while the general surface is not particularly sensitive to temperatures about 50° C, certain spots will be found where this stimulus produces a stinging pain. It would seem then that these spots are in reality heat spots, their true quality being masked by the phenomenon of intensification. As recovery progresses and the sensation "hot" is beginning to be felt locally the peripherally referred sensation which accompanies it may still be one of stinging pain only.[1]

The three outstanding peculiarities of returning thermal sensibility are the delay in the restoration of sensibility to heat and the intensification and peripheral reference of the sensation of cold elicited from the cold spots. When cold spots first reappear they tend in spite of the intense sensations they are capable of giving rise to, to shew a certain hypoaesthesia; that is to say they may be of less than normal activity in regard to discrimination and to the recognition of temperature but little below that of the skin. The intensification and the peripheral reference then, are phenomena superadded to the series of changes constituting recovery rather than interposed among them as a necessary stage. It thus happens that they persist long after recovery is otherwise complete. Then very gradually the intensity of the cold sensations diminishes though peripheral reference of them may last still longer. In one of the areas which we investigated 5 years after the nerve section and at a time when the most delicate examination revealed no defect of sensory acuity whatever, there was distinct peripheral reference of sensations

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[1] This statement applies to stimulation made with test cylinders 1 mm in diameter. When a stimulating object of large surface is used peripheral reference of heat is distinct.

of cold and although these sensations had lost their former startling intensity they were very distinct.

e) *Return of Sensibility to Pain.*

The return of sensibility to pain shews all the phenomena of recovery, namely hypoaesthesia, intensification and peripheral reference. In order to make quite clear the results of our observations a few preliminary considerations must be dealt with.

The investigation of sensibility to pain is sometimes made by using the prick of a needle as a stimulus. As we have already pointed out in dealing with tactile sensibility a stimulus capable of minute graduation is essential in the detailed investigation of any sensory change and it is this fact which renders the use of the needle quite unsuitable for fine work. Various algometers have been invented from time to time but none of them have been found wholly satisfactory. Those making use of a pin prick as stimulus are undoubtedly the least unsatisfactory: but the method of graduating the pressure applied is in most forms complicated and in some unreliable. No method of graduating small pressures more satisfactory than the *von Frey* hairs has come to our knowledge, and we found that by applying it to graduate the force of pin pricks a simple and practical algometer could be made.

In the quiet period immediately preceding the first evidences of recovery sensibility to pain shews a central area of complete loss surrounded by a zone of partial loss. If this hypoalgesic zone be tested with the hair algometer it is found that the nearer a given spot is to the central analgesia the stronger is the pressure upon the needle necessary to elicit the sensation of pain, and conversely the farther from the central area the spot stimulated, the nearer is the stimulus pressure to that which elicits pain when applied to the normal skin. The sensations produced in this hypoalgesic zone are qualitatively perfectly normal. There is about them no abnormal unpleasantness whatever and their sole difference from sensations elicited by stimulation of the normal skin is that they need a stronger stimulus to call them forth. This absence of any abnormal quality makes very striking the first appearance of recovery because the quality of returning sensibility to pain is markedly abnormal. The first appearances of restoration begin about the same time as do those of sensibility to touch. In the most proximal part of the affected area pin pricks now call forth sensations of pain which are abnormally unpleasant and are referred to the peripheral part of the area. The unpleasant quality of these pain sensations is very distinct; it causes the subject of them to feel a scarcely controllable impulse to move the part and a strong inclination to rub, not the place where the stimulus has been given, but the place to which the sensation was referred. It is a remarkable fact that this rubbing of the seat of peripheral reference, although the latter may be a foot or more away from the spot to which the stimulus was applied does give considerable relief. It is thus clear that there is some relation between the phenomena of intensification and peripheral reference. At first at any given spot this returning sensibility to pain is distinctly hypoaesthetic, that is to say although the stimulus pressure used now yields a sensation where previously it yielded none yet such pressure has to be stronger than that necessary to call forth a sensation when applied to normal skin. In process of time sensibility to pain spreads throughout the affected

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area retaining however its abnormal qualities but gradually becoming less and less hypoalgesic. There is no observable relation between hypoalgesia and abnormal quality; in fact the latter persists for months or even years after normal sensory acuity has been obtained.

f) *Summary.*

We are now in a position to state summarily the characteristics of sensibility accompanying restoration of function due to the regeneration of a nerve. These may be stated in the following propositions:

1. All forms of sensibility tend to reappear together, except sensibility to temperatures above that of the skin which is somewhat delayed; this delay is probably in part, at any rate, due to the difficulty of demonstrating sensibility to heat in its hypoaesthetic form, and to the effects of intensification.

2. All returning sensibility is at first hypoaesthetic.

3. All returning sensibility shews the phenomena of Intensification and Peripheral Reference.

4. Intensification and Peripheral Reference bear no relation to hypoaesthesia and persist long after restoration of sensory acuity is complete.

Observations of Head and his collaborators.

The observations of Head upon the special physiology of the peripheral nerves and the conclusions he draws from them are embodied in a series of bulky and elaborate contributions, some of which are wholly devoted to the subject while others contain more or less detailed reference to it. The list of papers is as follows.

The Afferent Nervous System from a New Aspect. Head, Rivers and Sherren. Brain, Nov. 1905.

The Consequences of Injury to the Peripheral Nerves in Man. Head and Sherren. Brain, Nov. 1905.

The Grouping of Afferent Impulses within the Spinal Cord. Head and Thompson. Brain, March 1907.

A Human Experiment in Nerve Division. Rivers and Head. Brain, Nov. 1908.

Sensory Disturbances from Cerebral Lesions. Head and Holmes. Brain, Nov. 1911.

Two only of these are entirely concerned with the results of the production in Head himself of an area of sensory defect by experimental nerve section. The first of these contains a general exposition of the interesting hypothesis which this experiment had led him to form, while the second comprises a detailed statement of the investigation and a discussion of various matters rising out of it.

The other three articles do not directly concern us here as the facts of observation they contain are derived from the clinical investigation of patients and are therefore by common consent of inconsiderable value as physiological data. In so far however as they do deal with matters of general principle we shall have to refer to various passages in them.[1]

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[1] In referring to the observations and conclusions recorded in these various contributions we shall for convenience use the name of Head only, without discriminating in each instance with which of his collaborators the particular work in question was done.

a) *Tactile Sensibility.*

One of the most striking of Head's observations was that recovery of sensibility to tactile stimuli began very much later than recovery of sensibility to thermal and painful stimuli.

"*Forty three days* after the operation the extent of the cutaneous analgesia had begun to diminish."

"*One hundred and sixty one days* after the operation cotton wool began to produce a diffuse tingling sensation over the forearm when the hairs were stimulated, but the whole of the affected area still remained insensitive to *von Frey's* tactile hairs."

"*Two hundred and twenty five days* after the operation the hairs on the back of the hand responded with diffuse tingling to cotton wool but the whole affected area of the forearm and hand still remained insensitive to *von Frey's* tactile hairs. This sensibility to cotton wool disappeared at once if the arm was carefully shaved."

"*Three hundred and sixty five days* after the operation the proximal patch on the forearm began to be sensitive to cotton wool after shaving." A Human Experiment etc. p. 341.)

It is clear however that stimulation of hairs had yielded sensations a great deal earlier than the period mentioned above as is shewn by the following quotation.

"The hairs within the affected area of the forearm and hand remained totally intensitive to all forms of stimulation until 86 days after the operation. We then discovered that within the upper patch on the forearm lay four hairs from which a sensation was evoked by pulling. At a distinct interval after the hair was pulled *Head* experienced a slowly developing vague sensation which was neither definitely painful nor unpleasant. It died away and recurred as a painful sensation which faded and again recurred as pain. The sensibility of these four hairs varied greatly; but slow development and a tendency to recur were the most certain characteristics of the sensation evoked when they were stimulated. This mode of reaction of the hairs was the beginning of the gradual restitution of a certain form of sensibility" (ibid. p. 385). It would seem then that the facts observed by *Head* were that sensations could be elicited by powerful stimulation of the hairs (pulling) at an early period of recovery (86 days); that the hairs become more and more sensitive to stimulation until at 161 days the comparatively weak stimulus of cotton wool elicited sensations; but that it was not until much later that cotton wool applied to the skin itself was felt.

He observed certain peculiarities of the sensations yielded by stimulation of the hairs. For example he says, speaking of the period 254 days the operation" . . . no part of the affected area which possessed hairs failed to respond.

This response was of the same extraordinary character as that with which we became familiar when testing the hairs of the forearm and consisted of a general tingling. Not only was it diffused widely but a sensation was evoked which seemed to lie over parts of the affected area remote from the point of stimulation" (ibid. p. 386).

From the facts that an area in the condition described in the last quotation is, when hairy, sensitive to cotton wool but insensitive to the same stimulus when shaved, while normal skin remains sensitive to cotton wool after shaving; and from

the fact that the sensations elicited by stimulation of the hairs in such an abnormal area are of distinctly abnormal quality, *Head* draws the conclusion that the hairs in the recovering area at this period "had become endowed with a form of sensibility independent of that usually called light cutaneous touch" (ibid. p. 387).

As we shall see later he associates this hypothetically distinct "hair sensibility" with what he calls the "protopathic" system of nerve fibres, which he regards as distinct from the system — "epicritic" — which subserves ordinary tactile sensibility. The process of recovery of sensibility to light touches is therefore according to *Head* somewhat complex; a peculiar form of sensibility to light touches returns first to the hairs and then after a long interval, sensibility to light touches returns to the skin itself.

When *Head's* observations on this subject and our own are compared the outstanding feature is the direct conflict of fact as to the time when tactile sensibility first reappears. According to us it returns about the same time as other forms of sensibility and often as the first manifestation of recovery, whereas according to *Head* it is very late and did not reappear in his own case for 12 months. Fortunately a good deal of light is thrown on this discrepancy by *Head's* own observations on hair sensibility.

In giving our own results we have insisted that tactile sensibility, like all other forms of sensibility, returns at first in a hypoaesthetic form; that is to say there will be a period during recovery in which the sensations characteristic of light touch can be elicited but only with a stimulus adequate for a threshold higher than that of the normal skin. With the use of such stronger stimuli (the heavier *von Frey* hairs) we have demonstrated repeatedly the reappearance of tactile sensibility between 80 and 90 days after the operation, just at the period that is to say when *Head* found that mechanical stimulation of the hairs gave rise to sensations and at a period of course when stimuli about the normal threshold, e. g. cotton wool, were not felt. It is of some interest that while *Head* insists repeatedly upon the fact that sensibility to pain and sensibility to thermal stimuli return at first in a hypoaesthetic form, that is with a high threshold, he did not, as far as we are aware make any thorough investigation of the possibility that tactile sensibility might also be returning in a hypoaesthetic form. His investigations of tactile sensibility seem to have been carried out chiefly with the use of cotton wool as a stimulus and to some extent with the lighter *von Frey* hairs. In regard to the use of the latter we can find no reference to his having investigated the area inside the line of cotton wool anaesthesia with any tactile hair exerting a pressure of more than 360 millegrammes which is about the normal threshold stimulus. As however he carried out his earlier investigations without the preliminary shaving which he later realised to be necessary for exact work, he did in fact accidentally use a stimulus far above the normal threshold. It had been shewn by *von Frey* 9 years earlier in his classical researches on tactile sensibility that the touch spots are localised in the region of the hair bulbs, and that these touch spots can be stimulated by pressure upon the skin near the hair or by movement communicated to the hair itself, and that the latter mode of stimulation yields sensations to a stimulus of much lower strength than does the former. *von Freys* says: „Ich habe schon in meiner ersten Mitteilung erwähnt, daß die schwächsten überhaupt noch wirksamen

Druckreize bei Berührung der Haare wahrgenommen werden. Die Schwelle des Haares liegt beträchtlich unter der seines Balges. So fanden sich z. B. für 6 bereits gekürzte Haare des Oberschenkels folgende Reizschwellen:

Haar	Reizschwelle des Haares	Reizschwelle des Haarbalges
I	I	12
2	3	17
3	5	12
4	5	12
5	5	12
6	5	33

Da nun die Reizschwelle des Haares sich um so mehr der seines Balges bzw. seines Druckpunktes nähert, je kürzer es geschnitten wird, um schließlich bei glatt rasiertem Haar mit letzterem zusammenzufallen, so muß man schließen, daß in beiden Fällen dasselbe Organ gereizt wird, vom Haare aus, der Hebelwirkung entsprechend, aber mit geringeren Kräften." (Beiträge zur Physiologie des Schmerzsinns. Zweite Mitteilung. Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft der Wissenschaften. 1895.)

We have ourselves obtained similar results. The following table is a characteristic example chosen from our records of such investigations.

Normal skin of Left Forearm.

Elastic pressure of *von Frey* hair in millegrammes		Stimulation of Hair Bulbs						Stimulation of Hairs themselves		
		10	22	40	70	140	230	10	22	40
No.: of Hair Bulb and Hair	1.	o	o	X	X	X	X		X	X
	2.	X?	o	o?	o?	X?	X		o	X
	3.	o	o	o	X?	X	X		X	X
	4.	o	o	X?	X	X	X	At least ¼ of the hairs reacted to this stimulus	X	X
	5.	o	o	X?	X?	X	X		o	X
	6.	X?	o	X?	X	X	X		X	X
	7.	o	o	X?	o	X?	X		X	X
	8.	o	o	o?	o	X	X?		o	X

o denotes no sensation felt.   X denotes sensation of touch felt.

It is therefore obvious that by stimulating the unshaved recovering area with cotton wool *Head* was applying a stimulus a good deal above the threshold of the shaved skin, hence as tactile sensibility was present only in a hypoaesthetic form, he got a reaction before shaving but not after. The reaction he got moreover shewed the characteristics which we have described as accompanying returning tactile sensibility namely intensification and peripheral reference. Furthermore in the earliest stages of recovery when he applied a much more intense stimulus by pulling the hairs, he was able to get a reaction 86 days after the operation. This corresponds closely with what we ourselves found in regard to the first appearance of tactile sensation in response to gross stimulation of a recovering area. Such stimulation for example yielded tactile sensations in two of our areas at 82 and 90 days respectively after the nerve section.

It seems to us therefore that the facts are capable of a simpler explanation than that offered by *Head*. In our opinion it is not possible to accept as established the supposed great delay in the return of tactile sensibility, or the equally remarkable acquisition by the hairs of a recovering area of the "form of sensibility independent of that usually called light cutaneous touch". That sensibility to tactile stimuli begins to return with the other kinds of sensibility and like them all in a hypo-aesthetic form at first, is to our mind a well established fact and one accessible to complete methods of examination.

b) *Weber's Test.*

In *Head's* observations there was a close relation between tactile sensibility and the capacity to discriminate two simultaneous touches. Before recovery began he "was entirely unable to discriminate one from two points of the compasses even when separated for the widest distance permitted by the size of the affected area on the hand, 6 cm in a direction longitudinal to the axis of the limb. And yet over a similar part of the normal hand a perfect record was attained at 2 cm" (Human Experiment etc. p. 364). Moreover during recovery he found that this inability to discriminate the two compass points "except at distances enormously in excess of the normal" persisted until the return of sensibility to cotton wool stimulation.

There is considerable discrepancy between these observations and our own results. We found that discrimination was impossible only in areas of such profound anaesthesia that even firm pressure could not be felt, as for example over the inner surface of the tibia in the case of the Internal Saphenous nerve area. Outside such regions but within the boundary of anaesthesia to cotton wool we never found total loss of discriminatory capacity but merely a reduction of it so that an increase in the separation of the compass points yielded results which shewed a distinct degree of sensitiveness. For example the normal skin around one area responded to a separation of 25 mm; the skin in the zone of gradually deepening hypoaesthesia within the line of anaesthesia to cotton wool gave, with the same separation, results which were very poor. With a separation of 50 mm however the results were nearly as good as of those of the normal skin at 25 mm. Testing the same area of skin before and after section of the nerve supplying it was another method used. The area presumably supplied the by nerve which was to be cut was sub-divided into segments and each of these separately tested with the compasses. After the operation such of these segments as fell within the limits of sensory defect were again tested. One such segment of the great auricular area gave before the operation out of 120 touches (single and double irregularly mixed) 84 right and 36 wrong: while after the operation it gave 75 right and 45 wrong. A segment fo the internal saphenous area similarly tested gave before the operation 85 right and 35 wrong and after the operation 72 right and 48 wrong. In both cases the separation of the compass points was the same throughout.[1]

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[1] During recovery the difficulty of compass testing is, as Head has pointed out, rendered very great by the phenomenon of reference which tends to make many of the single touches appear as double. Hence in the foregoing discussion we have not embodied any results of compass testing carried out on recovering areas.

Our observations then do not enable us to confirm *Head's* view that defects of tactile acuity and of discrimination of two simultaneous touches are always closely associated, or that sensibility to cotton-wool stimulation is invariably accompanied by inability to discriminate simultaneous touches. Section of a purely cutaneous nerve does undoubtedly diminish discriminatory capacity, but we have found time after time as the figures given above clearly shew, discrimination not very much below the normal in regions which were quite anaesthetic to stimulation with cotton wool. This conflict of evidence has led us naturally to examine somewhat closely the methods *Head* describes as having been used in his own case. His description is a detailed one and the precautions taken to exclude fallacy were numerous and stringent though it seems to us they were not altogether complete. In discussing methods of examination *Rivers* and *Head* say "Since *Head* was at the same time collaborator and patient we took unusual precautions to avoid the possibility of suggestion. No questions were asked until the termination of a series of tests; for we found it was scarcely possible in the long run to ask even simple questions without giving a suggestion either for or against the right answer. Sounds and movements that would have conveyed no information to an ordinary person would disturb *Head's* judgment in a case requiring fine discrimination . . . Towards the end of a series of observations with finer tests over an area of defective sensibility *Head* would frequently become uncertain in his answers because he had forgotten his sensations with the coarse forms of the same stimuli. He might for instance speak of contact with the neutral tube as warm. But occasional unexpected stimulation with the tube at 38° C would at once correct this tendency, and throughout the further observations the neutral tube would be recognised with certainty. After a long series of "double ones" the application of the compasses widely separated so as to produce a definite sensation of two points frequently produced a similar steadying effect" (Human Experiments etc. p. 345).

The latter paragraph indicates very well how great are the difficulties in securing the subject from receiving hints as to whether his answers are right or wrong. At first sight the procedure indicated might seem to one unaccustomed to such work comparatively harmless. A little consideration however will shew that the sudden interposition of a stimulus of unmistakeable intensity not only reminds the subject of the sensation-quality he has become uncertain of, but also acts as a signal informing him in the plainest possible terms that he is answering incorrectly. It is difficult to see how such signalling to the subject can be any less disturbing to the quality of the results than would be telling him in so many words that his answers were wrong. Indeed there is reason to suspect that the tendency to error would be greater than if the patient were clearly and simply warned that his responses were becoming grossly wrong. For not only are subject and investigator in a condition of false security as to the value of their methods but the information unwittingly given is suggesting in the case quoted not merely error in general but error in one special direction.

c) *Thermal Sensibility.*

In regard to the restoration of sensibility to thermal stimuli there is a fairly close correspondence between *Head's* observations and our own. He observed the

phenomena of intensification and peripheral reference, the slower restoration of sensibility to temperatures above that of the skin, and the tendency of the intensification of heat sensations to cause stinging pain to replace true sensations of heat. He also observed that in the early stages of recovery the skin was a good deal less sensitive to temperatures near its own than is the normal skin. He did not regard this however as the expression of a mere hypoaesthesia, but adopted the more complex interpretation that it was due to the absence from the skin of a special mechanism solely concerned with the appreciation of temperatures covering a range of not more than 10 to 12 degrees centigrade of the thermometric scale. The remarkable nature of this hypothesis is rendered more evident when it is remembered that sensations elicited in the normal by temperatures within this range are extremely faint and that temperatures occupying about 5 degrees at the middle of this range can arouse no thermal sensation at all. It seems probable that *Head* did not realise the existence of this normal intermediate thermoanaesthesia, for he speaks of a "neutral point of thermal sensibility" as if he regarded the skin as capable of yielding an unbroken series of sensations corresponding with the thermo-metric scale. We shewed in 1909 that this was not the case, that there was always present in the normal an insensibility to temperatures within a few degrees of that of the skin and that the chief way in which a thermo-hypoaesthesia manifests itself is by an expansion of this intermediate zone.[1])

d) *Sensibility to Pain.*

In regard to the recovery of this form of sensibility there is a close general correspondence between our results and those of *Head*. He observed the phenomena of intensification, peripheral reference and the fact that in spite of the intense sensations which were yielded, the threshold was in the early stages abnormally high.

There is however one respect in which there is a considerable discrepancy between our results and his. He found that the phenomena of intensification and peripheral reference bore a remarkable relation to the return of tactile sensibility, in that when the latter had recovered so far as to yield sensations to stimulation with cotton wool the former underwent a diminution so rapid that he was led to assert that the return of sensibility to cotton wool caused the disappearance of intensification and peripheral reference. As we have already repeatedly stated in none of the seven separate experiments in nerve division which we made did we find that these two phenomena bore any such relation to the recovery of sensory acuity. In the areas where acuity was completely restored intensification and peripheral reference of tactile, thermal and painful sensations persisted for many months or years afterwards and faded very slowly without shewing any relation whatever to the other features of sensibility.

e) *Comparison of the Phenomena observed before and during Recovery.*

In the theoretical conclusions of *Head* great importance is attached to the resemblances he observed between the state of sensibility following upon the nerve section and that accompanying recovery.

[1]) In a recent paper "Sensory Disturbances from Cerebral Lesions", in dealing with normal thermal sensibility, Head no longer speaks of a "neutral point" but of a "neutral zone" which he defines as occupying from 2 to 5 degrees Centigrade of the thermo-metric scale.

As there is considerable discrepancy between his results and ours it is necessary for us to discuss the subject in some detail. According to *Head* section of a cutaneous sensory nerve produces (1) a central area in which there is loss of all forms of cutaneous sensibility and (2) a zone surrounding this in which the sensory loss comprises tactile sensibility, the capacity to discriminate two simultaneous touches and thermal sensibility for intermediate temperatures, that is to say temperatures between 26° C and 37° C. This region he calls the intermediate zone, and within it are retained sensibility to pain and sensibility to temperatures below 26° C and above 37° C. When he says that there is loss of tactile sensibility throughout the whole area (intermediate zone and central region) he takes loss of sensibility to cotton wool touches as the criterion of this and the line at which this loss occurs as the outermost limit of the changes found. Proceeding inwards from this line, he finds a narrow irregular zone in which, while there is insensibility to cotton wool, to intermediate temperatures and to *Weber's* test, there is sensibility to extreme temperatures and to pain. The pain sensations elicited here are abnormally intense, tend to be diffuse and radiating, abnormally unpleasant in quality and to cause the subject a scarcely resistible inclination to make some motor response such as withdrawing or rubbing the part.

The intermediate zone may be extremely narrow and may in places be absent altogether: in the latter case the whole area is insensitive to painful stimuli, the margins of insensibility to cotton wool and to pin pricks coinciding.

When recovery begins the intermediate zone gets larger at the expense of the central area which now begins to be sensitive to pin pricks and to extreme temperatures but remains for a considerable time (12 months) insensitive to cotton wool. The quality of the sensations elicited by pin pricks over regions in this first stage of recovery is the same as that previously felt in the intermediate zone. It is this identification of the sensory qualities of the recovering area and of the intermediate zone which forms one of the principal foundations of *Head's* hypothesis as to the constitution of the peripheral nerves.

The existence of this supposed identity we have been entirely unable to confirm.

It is clear that in order to be able satisfactorily to compare two sensory qualities, both of them abnormal, the subject should possess at one and the same time distinct areas due to the division of separate nerves in one of which recovery is in progress while in the other recovery has not begun. Unless this be possible either an undue reliance must be put on the memory of the subject, or there can be no certain guarantee that the sensibility in the part of the area supposed not yet to shew recovery is in fact entirely uninfluenced by regeneration. It has always been evident that the essential difficulty in accepting the more far reaching of *Head's* conclusions is that they are based upon a single experiment in nerve division and on the experiences of a single subject. We ourselves found that in investigating the effects of each one of the first six separate experiments which we made, we learnt many new refinements of technique and were able to take fuller and fuller advantage of the opportunities offered by each new area; and it was not until the seventh nerve section that we felt that our methods and experience were so thoroughly organised that we could use the final experiment as a confirmatory test for our previous

results. It should be remembered that the time at *Head's* disposal for the investigation of the changes following nerve section but preceding recovery, was limited to 6 weeks and that a very large amount of important and elaborate investigation had to be got through in this time. Now hyper-sensitiveness to painful stimuli following the nerve section and preceding recovery proved in our experience to be a very baffling phenomenon and one calling for much intricate investigation. To trace any uniformities in its occurrence and behaviour we found to be scarcely possible in connection with the first two nerves we divided and apart from learning that it certainly could not be generalised in the simple way indicated by *Head* we made little progress. With the knowledge gained by the later experiments certain uniformities did however become perceptible. Of these by far the most important and the most significant as regards its bearing on general principles was the fact that hypersensitiveness to pain in the area of the divided nerve was, when it occurred, essentially a transient phenomenon, always disappearing completely before there was any trace of recovery in the functions of the nerve, so that a quiet interval of at least a month was invariably to be observed before recovery began. In this interval there was never any trace of hypersensitiveness to pain. The affection of sensibility to pain now shewed a central area of profound loss surrounded by a zone of partial loss, the hypoalgesia being most marked towards the centre of the area and least marked at its periphery. We wish to state once more and with the strongest possible emphasis that during the quiet interval we have already defined this hypoalgesic zone never yielded sensations of pain either radiative or of abnormal unpleasantness. We have described elsewhere ("Experimental Studies" etc.) the details of the circumstances under which hypersensitiveness to pain may appear after section of the nerve. It is enough to say here that the distribution of it is always in irregular patches which shew an unmistakeable tendency to appear in the neighbourhood of subcutaneous veins and to have remarkably little relation to the distribution of defects in sensibility. It is not limited to the intermediate zone of *Head* and tends to overstep both the inner and outer margins of this but more especially the latter. The second fact of importance in this matter is that this irregularly patchy hypersensitiveness makes its first appearance about the 10th day after the operation, reaches its maximum in about a week and then begins to fade so that by the 6th week it can scarcely be detected anywhere and the characteristically stable condition of analgesia and surrounding hypoalgesia is definitively established. Thirdly by sufficiently delicate algometric observations a most important distinction can be made out between the transient hypersensitiveness to pain and the hypersensitiveness characteristic of recovery. The former is a true hyperalgesia that is to say has an abnormally low stimulus threshold, while the latter is merely an intensification of the response to stimulation and bears no direct relation to the degree of sensory acuity present at the time. Fourthly the sensations of pain elicited from patches of this transient hyperalgesia although abnormally unpleasant and tending to be somewhat diffuse have never in any single instance in our experience shewn anything in the remotest degree resembling peripheral reference. It will thus be seen that the whole of our experience gathered from two subjects and from areas in many different parts of the body is unable to afford the least support for the view that such hyperalgesia as occurs

before the appearance of recovery is in any way related to the intensification of painful sensations found in a recovering area.

The resemblances which he describes as existing between the intermediate zone and the early recovering area *Head* supposes to be due to these regions being supplied by a special set of nerve fibres which is concerned with sensibility to pain and to extreme temperatures. In any given nerve the fibres concerned with this group of sensations tend to supply a smaller area than that supplied with fibres which subserve sensibility to touch and to intermediate temperatures. Consequently when the nerve is cut the difference between the areas of the two kinds of nerve fibres is the intermediate zone, which is thus supposed to be an area of uniform sensibility of a special kind ("protopathic").

As we have already stated, in none of our experiments did we find such uniformity. On the contrary in each case we found that the region corresponding with the intermediate zone of *Head* was one of hypoaesthesia steadily increasing in degree when it was explored from the periphery towards the centre. So that for example while in the outer part the thermo-hypoaesthesia appeared as a slight increase of the normal indifference to intermediate temperatures, towards the inner part only the very faintest thermal sensations could be elicited with any temperature. There was therefore in our observations no evidence to encourage the belief that section of a cutaneous nerve can produce a specific and clearly marked loss of sensibility to temperatures from $26°$ C to $37°$ C. There is reason to suppose that *Head* was not at all advantageously placed for the investigation of the sensibility of the intermediate zone. In addition to the limitation of the available time imposed by the restriction of the work to a single experiment, it would seem that in his case, as it happened, the actual area of intermediate zone was extremely small. *Rivers* and *Head* say for example "In our case we had even less opportunity than usual for studying the primary dissociation of cutaneous sensibility. For on the anterior surface of the forearm the loss of sensation to prick and to cotton wool corresponded exactly. Towards the radial aspect its boundaries were ill-defined to both stimuli, merging gradually into parts of normal sensibility. But over the back of the hand lay a narrow border 2 mm in breadth insensitive to cotton wool but sensitive to prick" (Human Experiment p. 368). A region so limited as this cannot to our minds be regarded as capable of yielding altogether satisfactory results as to the true nature of sensibility in the intermediate zone. It is true that another area presumably of intermediate zone type was discovered.

"Within three weeks of the operation (op. cit. p. 369) another small dissociated zone appeared in the first interosseous space around the distal border of the affected area. Here sensibility to painful cutaneous stimuli was so low that they were followed by no increased reaction. A prick produced a slowly developed dull aching different from the exaggerated discomfort evoked on stimulating the border on the back of the hand. Moreover this small area in the interosseous space was insensitive to all thermal stimuli and neither cold nor heat spots could be discovered within it. It was evidently so little sensitive to protopathic stimuli that the skin could respond to painful stimulation only and even this response was extremely feeble."

It is plain that this segment of the intermediate zone cannot have contributed evidence that the intermediate zone is endowed with sensibility to extremes of temperature and to pain, and that the sensations of pain elicited within it are abnormally unpleasant and accompanied by an excessive motor reaction.

Recovery occurs according to *Head* by the appearance throughout the area of the form of sensibility which is found after the operation in the intermediate zone. This is owing to the fact that the nerve fibres concerned with sensibility to pain and to extreme temperatures regenerate first. After these have completely regenerated there is a considerable pause and then the fibres concerned with sensibility to touch and to intermediate temperatures regenerate and restore sensibility to the normal. When this event occurs the characters peculiar to the first form of sensibility (intensification and peripheral reference) disappear owing to their being inhibited by the restoration of the second form of sensibility. Furthermore restoration of the second form of sensibility (touch and intermediate temperatures) may be incomplete leaving a part of the area permanently supplied with the first form of sensibility only. From such a statement of the facts our results shew divergences which seem to be essential. Most of these have already been stated but it is necessary that we should add something here on the subject of incomplete recovery. Incomplete recovery is undoubtedly common but the evidence we have accumulated shews that there is no special tendency for sensibility to return in two well defined groups or for one group to return alone. If owing to incomplete recovery some part of the area remains permanently hypoaesthetic there is no tendency for the hypoaesthesia to touch to be particularly marked. Moreover in a large area some part may shew a permanent failure of recovery of all forms of sensibility. *Failure of recovery then, according to our observations, is in no sense selective for different forms of sensibility, and appears in such a way as to suggest that it is due to some general obstacle to regeneration rather than to a hypothetical difference in regenerative energy possessed by nerve fibres of different functions.* The impression that sensibility to pain and to extreme temperatures, specially cold, recover earlier than sensibility to touch might very easily be gained even after a fairly thorough examination because the picture presented by a recovering area is dominated in so remarkable a way by the phenomena of intensification and peripheral reference which are especially marked for sensations of cold and pain. As we have already seen the apparent delay in the restoration of sensibility to heat is probably due to the exaggeration of the pain factor in the sensation "hot" by intensification, and we have pointed out that similar qualities in returning sensibility to touch led *Head* to assume the existence of a hypothetical "hair sensibility". It would seem that intensification and peripheral reference must be dealt with as phenomena unrelated to the recovery of sensory acuity for we found no evidence that they underwent any sudden and striking diminution when an area recovered sensibility to cotton wool touches, but might be recognisable years after this period. We cannot therefore confirm *Head's* attempt to identify them with special forms of sensibility and we could find no evidence of their being "inhibited" by the reappearance of any other form of sensibility. So little in fact is peripheral reference inhibited by returning sensibility to touch, that touch sensations themselves shew the phenomenon in its most exquisite form.

Head's hypothesis of the constitution of the peripheral nerves.

However great may be the differences between the observations of *Head* and of ourselves and we have shewn above that they are considerable, the fact is established by both series of investigations that during recovery after section of a cutaneous nerve, the affected area shews certain very remarkable peculiarities of sensibility. These peculiarities can as we have shewn be narrowed down to the phenomena of intensification and peripheral reference. In addition to their directly practical importance intensification and peripheral reference are matters of great theoretical interest. To the subject of them they present a series of sensations entirely new and altogether outside his previous sensory experience, and yet they are surprisingly definite and unmistakeable. No one who has not experienced them can appreciate the intense vividness with which they present themselves to the subject; and the investigator with no direct knowledge of them is likely even to be wearied by the importance their brilliance makes them assume in the subject's mind.

It has been suggested by authorities whose opinions are entitled to very respectful consideration (*von Frey, Mackenzie*) that these peculiarities of recovering sensibility are of central origin and possibly due to changes in the central nervous system consequent upon the nerve section. It is clear that this possibility is one which should not be overlooked but it must be admitted that at the present time but little positive evidence bearing upon it has been accumulated.

The hypothesis which has been put forward in the greatest detail is that of *Head* who first observed the phenomena under experimental conditions. This hypothesis was first enunciated in 1905 in a paper containing a summary account of observations upon an area of sensory loss experimentally produced upon the writer's arm. It was expounded in greater detail in a paper dealing with the same observations in 1908. Not long after, our own observations were also published. Although it was clear that there were profound discrepancies not only between the interpretations but also between the facts as recorded by *Head* and ourselves, we felt that a detailed criticism of *Head's* hypothesis would then be premature and contented ourselves with pointing out some of the more obvious difficulties in accepting some of his facts and many of his conclusions. Since that time the divergences between our views and his have in no essential particular diminished and no evidence has been produced which seems to us to disprove or to explain away the observations we then described. It seems therefore desirable to take advantage of the opportunity now presented to attempt some more fundamental criticism than we have yet entered upon. A short exposition of *Head's* hypothesis is first necessary. According to him the skin is supplied by two distinct systems of nerves which endow it with

1. "Protopathic sensibility capable of responding to painful cutaneous stimuli and to the extremes of heat and cold. This is the great reflex system producing a rapid widely diffused response unaccompanied by a definite appreciation of the locality of the spot stimulated.

2. Epicritic sensibility by which we gain the power of cutaneous localisation, of the discrimination of two points and of the finer grades of temperature called cool and warm."

According to this view the peculiarities of the early recovering area are due to the fact that it is innervated solely with protopathic nerves which regenerate more easily and more rapidly than the epicritic. As soon as epicritic sensibility returns, which is several months later, the peculiarities of the early recovering area disappear. As *Head* says (Human Experiment p. 448) "When once a part of the body is endowed with epicritic sensibility reference ceases entirely." Any given cutaneous nerve tends to supply epicritic sensibility to a larger area than that to which it supplies protopathic sensibility. Consequently when the nerve is cut the area of epicritic loss is larger than that of protopathic loss and consequently there is a region more or less extensive inside the boundary of epicritic loss which is still supplied with protopathic sensibility. This is the intermediate zone and as it is possessed of protopathic sensibility the sensations elicited from it are essentialy the same as those elicited from an early recovering area. Protopathic sensibility is of a more primitive and less developed nature than epicritic sensibility and represents an earlier stage in the developmental history of the nervous system. There is one area on the surface of the body, the glans penis, which is normally endowed with protopathic sensibility only. The internal organs are supplied with protopathic sensibility and the referred pain which is sometimes met with in visceral disease is a phenomenon of the same order as the peripheral reference of a recovering area. It is a simple corollary from this hypothesis that the intermediate zone after nerve section, the early recovering area, the glans penis and the viscera are all endowed with sensibility of the same type and that the sensations elicited from them are in essence of identical characters.

The detailed exposition of the hypothesis does not present quite so symmetrical an appearance as do the general statements. For example the insensibility to intermediate temperatures presented by a protopathic area is sometimes referred to as ranging from $22°$ C to $40°$ C and sometimes as ranging from $26°$ C to $37°$ C; areas described as protopathic may be totally destitute of thermal sensibility, or while sensitive to cold may be insensitive to heat. Again it appears that protopathic sensibility is not entirely devoid of the capacity of responding to light touches, for comparatively early in recovery the hairs of the "protopathic" part were found to react to cotton wool. It is denied that this is sensibility to light touches and a special form of "hair sensibility" is postulated and assigned to the protopathic system. With regard to the reference of sensation the preciseness of the phenomenon as it occurs in the recovering area is brought out. In the intermediate zone however and on the glans penis there is no description of any precise reference and the sensations are merely described as being diffuse and no remark is made upon the total difference between the two conditions.

In view of these frequent slight ambiguities, no doubt merely in expression, the hypothesis when viewed in direct relation with the evidence acquires a certain indistinctness which renders closely reasoned criticism somewhat difficult.

In judging the acceptability of a hypothesis such as this it is necessary to keep clearly in mind that the considerations supporting it are derived from two entirely different sources which yield evidence of very different value. These different qualities of evidence may be described as the direct and the indirect. By the direct evidence we mean that collected under the specially favourable con-

ditions of the actual research itself from which, it may be supposed, the hypo-
thesis was a conclusion inductively drawn. Clearly such evidence is of far greater
value than any other and criticism of it must be directed either to the facts of ob-
servation or to the processes of induction leading to the hypothesis itself. By in-
direct evidence we mean the various corroborrative applications of the hypothesis
to facts not directly observed during the research, to supposed matters of common
knowledge or to other speculative conclusions. This second class although of notori-
ously slight evidential value is as is well known apt to acquire undue importance
in influencing one's judgment in favour of a given hypothesis. It is therefore of
great importance that this type of evidence should be dealt with separately in the
full realisation that its influence is usually in excess of its value.

In dealing with theoretical considerations concerned with the physiology of
the nervous system, one is exceptionally liable to be misled by preconceived or
introspectively evolved notions as to how sensory and perceptive processes may
be supposed to act. Symmetry and the desire for classification are apt to be mis-
taken for physiological principles and we tend to drift into the error of supposing
that conceptions which are clear cut, easily comprehensible and "reasonable".
acquire by that very fact an increased probability of being accurate expositions
of the physiological processes they profess to explain. This has been repeatedly
demonstrated in the history of neurology. A very good instance of it is shewn
in the development of the theory of aphasia. The earlier workers on the subject
evolved from the study of such of their mental processes as were accessible to intro-
spection certain very definite conceptions as to how the processes underlying the
mechanism of speech must work. Gradually a series of conceptions grew up which
derived their chief support not so much from contact with the facts of cerebral
pathology as from their inherent reasonableness, and it is quite lately that we have
begun to learn that physiological necessity is apt to defy our preconceived notions
of resonableness and to escape any classification which is more respectful of logic
than of fact.

When *Head* advances the conception of two forms of peripheral sensibility
one more primitive than the other and forming the sole sensory endowment of
an earlier type of organism, the idea is at first sight attractive. We are presented
with a picture of a creature of simple needs, possessed of a sensorium capable only
of informing him of powerful stimuli, these stimuli leading to bulky sensations
which call imperatively for immediate reaction. With further development and
increasing need for communication with the environment the second form of sens-
ibility appears, which while endowing the higher animal with the capacity for
appreciating more delicate stimuli inhibits the now unnecessary and harmful energetic
reaction to stimulation to which he was previously liable. The whole conception
is striking and ingenious but carries with it no internal corroboration. Scientific
criticism cannot regard it as making in any degree the existence of the two hypothe-
tical forms of sensibility more probable. We have no evidence that one form of
sensibility is biologically more primitive than the other, the sense of contact given
by tactile sensibility is as far as we know just as essential as the sense of pressure
obtained in the absence of it. While if we are to accept *Head's* view that peripheral
reference is an essential part of protopathic sensibility it is difficult to conceive

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a more dangerous endowment for any animal however primitive than the capacity to feel when it is injured a sensation of pain in some part of the body remote from the lesion.

On the other hand there are certain inherent difficulties in the acceptance of the hypothesis which cannot be overlooked in any general consideration of it. For example the whole problem is dealt with on the assumption that all the phenomena consequent on a section of the nerve whether they occur before or during regeneration are entirely those of loss of function. That the destruction of the nerve after it has been severed from its centre produces no effect upon the tissue in which it lies except the loss of sensibility and that the reinvasion of the affected area by the regenerating nerve produces no effect upon the invaded tissues except a restoration of sensibility seems to us a large and serious assumption which should not be made without critical enquiry.

Again the multiplication of sensory mechanisms assumed by the hypothesis is a feature upon which criticism may well be directed. The difficulty is sufficiently great when we find thermal sensibility divided between two entirely different mechanisms, the one dealing with temperatures between 26° C and 37° C, the other with temperatures outside this range. The difficulty seems even greater with regard to sensibility to touch; for we find that while ordinary tactile sensibility belongs to the epicritic system a peculiar form of "hair sensibility" also aroused by light touches, belongs to the protopathic system; so that while in the case of thermal sensibility the protopathic and the epicritic systems have distinct end organs of their own, with regard to sensibility to touch they both use the same end organs.

Such theoretical objections might be developed to a much greater extent but they are of secondary importance as compared with the criticism of the direct evidence upon which obviously the case must ultimately rest.

The facts of observation which form the basis of the hypothesis fall into two categories; first those derived from the study of an area of sensory defect experimentally produced, and secondly the occurrence normally of an area of skin which is supposed to be endowed with protopathic sensibility only. Of the facts of the first category, three are absolutely fundamental and upon the authentication of them the establishment of the hypothesis depends. These are:

1. The identification of the sensory conditions found before the beginning of recovery in the intermediate zone with those found in the early recovering area.

2. The absence of recovery of tactile sensibility during the period when sensibility to pain and to extreme temperatures is being restored.

3. The fact that the phenomena peculiar to sensibility in the early recovering area, namely intensification and peripheral reference are abolished by the restoration of tactile sensibility as measured by cotton wool stimulation.

We do not propose to recapitulate the evidence we have produced above in criticism of the validity of these supposed facts, but we may add a few words in general comment.

Our investigations were undertaken primarily with the desire of confirming *Head's* conclusions by the use of the method through the introduction of which he had so greatly enriched the resources of experimental physiology. Inclined as we were to accept his conclusions we felt that being founded upon a single experi-

ment, they could not be fully recognised without further experimental confirmation. It was only after the earlier experiments and when we had come to see that the attempt to reconcile the facts we were collecting with the principles of *Head* was leading to increasing difficulty and confusion, that we realised that the hypothesis put forward by him was not capable of generalising the facts.

It will be remembered that we have produced a good deal of evidence against the acceptability of each of the three facts we have enumerated above as fundamental to *Head's* conclusions, and we have shewn incidentally in many cases the probable mechanisme by which he was led to what we regard as incorrect inferences.

We now have to deal with the second group of facts of observation namely that based upon the sensory peculiarities of the glans penis which according to *Head* is a part of the body endowed with protopathic sensibility only.

In 1895 *von Frey* had fully described the sensibility of the glans penis. He found that the glans was insensitive to tactile stimuli, sensitive to painful stimuli and to a certain extent sensitive to thermal stimuli. The thermal sensibility was marked at the neck and corona of the glans but diminished rapidly from there towards the end of the organ to reappear in the neighbourhood of the meatus; midway between corona and meatus it was practically altogether absent. The frenum and the inner aspect of the prepuce had the usual sensibility of the skin. The pain elicited by appropriate stimulation over the glans was especially unpleasant and of a deep seated boring character. The thermal sensations at the neck and corona were very distinct. *Head* confirmed these results and added that such parts of the glans as had any thermal sensibility, namely the corona and immediately round the meatus, though sensitive to extreme temperatures were insensitive to intermediate temperatures. He concluded that the glans penis is, in addition to deep sensibility, endowed with protopathic only, and regarded it as a remarkable confirmation of his hypothesis that there should occur normally an area of skin where owing to the absence of epicritic sensibility the existence of protopathic sensibility was disclosed. We have already referred to the variability in the conditions to which the term protopathic sensibility is applied and this is to some extent a case in point. The fact that painful sensations produced by stimulation of the glans are described as deep seated and felt as if in the urethra is apparently taken as comparable with the phenomena of reference in a recovering area. Now one of the most striking facts about the latter phenomenon is that the referred sensation is invariably superficial and of a remarkably definite localisation. It is always possible for the subject to point with his finger to the exact spot where the referred sensation is felt. Again nothing is said about any similar reference of thermal sensations but if there is one fact more striking than another with regard to thermal sensibility in a recovering area, it is the extraordinarily vivid reference of sensations of cold. It would therefore be necessary to sacrifice the most striking peculiarity of "protopathic" sensibility if the sensibility of the glans penis were to be brought within that category. Supposing however that such objections could be overruled it may yet be asked whether we are justified in accepting the explanation put forward by *Head* of the sensory character of the glans penis or whether an explanation more consonant with the general body of physiological knowledge can be found.

Let us briefly recapitulate the facts. The glans penis is insensitive to touch but sensitive to pain; its general surface is insensitive to thermal stimuli but its margins are sensitive to them. Such thermal sensibility as is present however is of a diminished acuity, for we learn that even in what we may call the marginal regions (the corona and immediately round the meatus) intermediate temperatures are not appreciated. To explain such peculiarities the most obvious course would seem to be an enquiry into the embryological history of the part. Now the penis is completely formed and intrauterine life is far advanced before the prepuce is differentiated; there then begins near the meatus the ingrowth of a solid lamina of epithelium which cuts off the prepuce from the glans. This ingrowth of epithelium subsequently splits into two lamellae setting free the prepuce and furnishing the epidermal lining to it and the covering of the glans. The process is remarkable as occurring so late in foetal life; in fact it is frequently incomplete for some time after birth as shewn by the occurrence of the well known "adhesion" between prepuce and glans. This detachment of the skin of the glans at so late a period may well be supposed to exercise a profound effect upon the sensibility of the latter, and there is a remarkable coincidence between the distribution of this separation and that of the sensory peculiarities. The process begins around the meatus, therefore the actual neighbourhood of the meatus itself is unaffected; it is arrested at the corona and at the frenum so that the frenum and the parts central to the corona are of normal sensibility. Finally in the regions near where the process begins and ends (meatus and corona) we find thermal sensibility surviving for a short distance in an imperfect form. In face of an explanation so extremely simple we do not feel that it is necessary to invoke an hypothesis involving the whole structure of the peripheral nervous system to explain the sensory peculiarities of the glans penis.

On the significance of the phenomena observed during the recovery of sensory nerves.

When we published our observations in 1909 we did not feel that the facts justified our going in the direction of attempting to explain the peculiarities of recovering sensibility beyond hinting that the evidence seemed to point to some local peculiarity in the regenerating nerve trunk. Further experience and reconsideration of the facts seem now to justify some more definite expression of opinion. We may say at once that though certain modifications in our statement of some of the elements of the problem have become necessary, our opinion of the direction in which the solution lies has been confirmed. Any discussion of the matter to be at all effective must be prefaced by a statement in the clearest possible terms of the phenomena it is concerned with.

1. Facts of Observation.

During the process of recovery after section of a cutaneous nerve three groups of remarkable phenomena are to be observed. Two of these are concerned with sensibility in the recovering area, viz Intensification and Peripheral Reference. The third concerns the recovering nerve trunk between the point of section and the proximal boundary of the affected area. It consists in the possession by this length of nerve of a greatly increased accessibility to direct stimulation.

a) *The facts of Intensification.*

By intensification we mean that qualitative change in the sensations elicited from a recovering area which makes them abnormally vivid. The vividness is most marked in sensations of cold and sensations of pain and less marked in sensations of touch and sensations of heat; the difference probably does not indicate more than that the sensation of touch is by nature but little susceptible of magnification and the sensations of heat when intensified tend to be felt principally or wholly as pain. Intensification is intimately associated with peripheral reference in such a way that an intensified referred sensation may alone be felt, or may be felt in association with an intensified local sensation. Intensification frequently accompanies defects in sensory acuity but on the other hand it always persists long after sensory acuity is completely restored. For example, one area five years after section of the nerve and four years after restoration of sensory acuity, still shews intensification. The fact that the phenomenon is present throughout the whole period of recovery may lead to confusion in description unless this is especially guarded against. For example in the early stages of recovery when the threshold for pain is still high it would obviously be incorrect to describe the area as hyperalgesic however unpleasant the sensations elicited might be. On the other hand when the pain threshold has come down to the normal and a stimulus which just produces pain in the normal skin, produces a much more intense pain on the abnormal, the latter might fairly be described as hyperalgesic. In our earlier contribution we did in fact describe it as such but we now think that the use of the term hyperalgesia is better avoided in this connection because it is accurate only during a certain period of recovery. Even when pain can be elicited by a stimulus that does not cause pain on the normal skin as is the case when heat stimuli are used at a certain stage, it is safer not to use the term hyperalgesia otherwise the impression is given that there is a closer relation between sensory acuity and intensification than really obtains.

b) *The facts of Peripheral Reference.*

We use the term peripheral reference to indicate the peculiarity of recovering areas whereby sensations, instead of or in addition to being felt at the place stimulated, are felt in the distal part of the affected area. It is the earliest phenomenon of recovery and is characteristic of the first sensations of recovering sensibility such as can be elicited only with strong stimuli applied over the point where the nerve trunk enters the affected area. It is moreover the most persistent result of the nerve section, surviving years after the complete recovery of sensory acuity. In this respect it corresponds exactly with intensification with which it is very closely associated, for all sensations capable of intensification when they are peripherally referred are intensified. All sensations are capable of peripheral reference though all do not shew it with equal readiness. It is a very precise phenomenon for sensations of touch, of cold and of pain but it is difficult to demonstrate in regard to sensations of heat. If the investigation is limited to stimulation with metal cylinders having a small surface of contact (1 mm in diameter) it may be impossible to demonstrate peripheral reference of heat, because intensification causes the thermal factor in the referred sensation to be obscured by the pain factor. It was for this reason that in our earlier contribution we stated that we had been

unable to observe peripheral reference of a clear sensation of heat. Later investigation
has shewn that with the use of a large stimulating surface heat sensations are found
to behave as regards reference as do cold, touch and pain.

At an early stage, on stimulation of a given spot the referred sensation alone
is felt and there is a total absence of any local response. Later a local sensation
is felt in addition to the referred and both are equally clear and equally intensified.
Very gradually the intensification of both diminishes but up to the present time
none of the areas upon which we experimented has altogether lost peripheral refer-
ence. In a general way it may be stated that the seat of the referred sensation,
to whatever part of the area the stimulus may have been applied, is somewhere
in the most distal part of the region rendered anaesthetic by the nerve section.
It always extends up to the margin of the area. Now when a cutaneous nerve in
one of the limbs is cut the area of anaesthesia produced usually tapers towards
its distal extremity so that the region in which peripherally referred sensations
are felt tends to be much narrower than the more proximal parts of the area. The
consequence is that all the peripherally referred sensations are felt in the same
spot. When the area happens to have a relatively broad distal extremity it can be
shewn that the reference though always distal may to a certain extent be diagonal
as well. For example in the case of the internal saphenous where the whole area
is of great breadth stimulation of the anterior part of the area elicits a sensation
referred to the back of the malleolus while stimulation of the posterior part of
the area elicits a sensation referred to the front of the malleolus. In the case of the
great auricular nerve however the area of skin supplied is distributed with its long
axis at right angles to that of the nerve; peripheral reference here therefore shews
this spreading of the foci of reference very clearly and spots can be found along
the margin of the area to each of which sensations are referred from some special
part. A character common to all cases is that the actual region to which sensations
from a given part of an area are referred is always considerably smaller than the
area the stimulation of which yields the sensations. These statements as to reference
to small and distinct foci are true only so long as the stimulus used is not more than
moderately energetic. When the energy of the stimulus is greatly increased, by
increasing the area to which it is applied, the referred sensation spreads so as to
occupy the whole nerve area distal to the point stimulated. The phenomena of
peripheral reference are always to be obtained in their most marked form in the
near neighbourhood of the regenerating nerve. The facts of reference given thus
far are relatively simple and the statement of them includes all the most striking
phenomena.

There is however a further statement to be made in regard to a group of facts
which are much less conspicuous. When the process of recovery has reached the
distal half of a given area it is found that many of the sensations elicited by stimu-
lation here are referred proximally. These proximally referred sensations are much
less distinctly intensified than those peripherally referred and are felt to some
extent along the course of the regenerating nerve but chiefly at the point of nerve
section. This phenomenon is especially striking in the one case in which the point
of nerve section was no less than 6 inches proximal to the upper limit of the affected
area. At the stage when proximal reference has appeared stimulation of many

a spot in the distal part of the area will yield three distinct sensations namely local, peripheral and proximal. A similar spot may also yield a proximal sensation alone or peripheral and proximal sensations alone. It may be remarked in this connection that in the case of the great auricular nerve although proximal reference to the point of section was never observed, there were many spots which yielded sensations referred to two distinct regions such as one on the cheek and one on the ear.

c) *The facts of Increased Excitability of the Nerve Trunk.*

The third important group of phenomena accompanying recovery is that concerned with the increased excitability of the nerve trunk. Certain cutaneous nerves run a long superficial course before they reach the region to which they are distributed. Such a nerve as we have pointed out elsewhere can be localised and traced with great exactitude by exploring the surface of the skin with the faradic current. If the course of the nerve be ascertained and marked on the surface by some relatively permanent stain such as silver nitrate, a more or less extensive length of it between the point of nerve section and the proximal limit of the consequent anaesthesia will be available for investigation during the period of recovery. It will then be found that the regenerating nerve trunk responds to stimulation some time before the skin to which it is distributed has regained any of its sensibility.

In order that such investigation shall be satisfactory it is obvious that two conditions must be satisfied. First that the nerve must be subcutaneous so that it shall be accessible to stimuli of moderate energy and secondly that its course between the point of section and the point where it begins to be distributed to the skin shall be long, so that it may be certain that responses are due to stimulation of the nerve and not to stimulation of its end organs in the skin. In one experiment as already mentioned we were so fortunate as to find and divide a nerve (middle cutaneous of thigh) which had a superficial course below the point of section of as much as 6 inches before it began to be distributed to the skin. The nerve had been marked out on the surface before the operation so that during recovery we had an exceptionally good opportunity of investigating its sensibility under the most favourable circumstances. Investigation of this nerve shewed not only the earliest evidences of recovery but that it acquired as regeneration progressed a very remarkable increased accessibility to direct stimulation. The sensations elicited by stimulation of it were invariably referred to the area of distribution. If the stimulation was moderate the sensations were referred to the peripheral part of the area. Energetic stimulation however led to the sensations being felt throughout the whole area and possibly along the nerve trunk itself as well. This increased excitability was limited to the nerve below the point of section and never extended above it. The stimuli which were effective were the faradic current, touches, pain stimuli (thermal or mechanical), heat and cold. The specific quality of the sensation elicited by the various stimuli was perfectly clear and shewed intensification which was distinct but not so pronounced as that found in the recovering area itself. The specific quality was most unmistakeable of course in the case of cold, this being of all sensation, the one which is qualitatively the most characteristic. The latent period between the application of the stimulus and the perception of the sensation was in the case of cold of considerable length because of the time occupied

in the transmission of the thermal change through the skin. As might have been expected the results of stimulation with heat were more difficult to obtain and more elusive. Nevertheless they were perfectly definite and we are able to state that stimulation of a regenerating nerve with heat produces corresponding sensations in the recovering area.

The increased excitability of the nerve reached a very high grade so that for example ordinary punctate stimulation with cold easily produced typical sensations.

d) *On the excitability of normal nerve trunks.*

We have referred to these remarkable changes in the nerve trunk as an increased excitability rather than as an altogether new property of the regenerating tissue because it is an old observation that normal nerve trunks are excitable though to a much slighter degree. The observation upon which this knowledge is based seems to be the statement that if the elbow be held in iced water sufficiently long a sensation of cold will be felt in the area of distribution of the ulnar nerve. The observation does not seem to have been repeated very often and one may well suppose that it has proved discouraging, for the conditions of the experiment are as bad as they could well be. The nerve is not really subcutaneous so that the immersion of the part in iced water would have to be prolonged to produce the desired effect. Such prolonged and extreme cooling would lead to a local aching in the part intense enough to disturb the critical capacity of the most philosophic. If however subcutaneous nerves are chosen in a part comparatively free from fat, clear results can easily be obtained. The nerve we have found most suitable for the experiment is the musculo-cutaneous of the leg. In front of the ankle and on the dorsum of the foot the branches of this nerve can be readily seen and felt so that stimuli can be applied to them with certainty. There is therefore little or no difficulty in demonstrating that the nerve trunk is sensitive to stimulation with cold and that the resulting sensations are felt according to the energy of the stimulus in the peripheral part of or throughout the area of distribution. The only other stimulus to which normal nerves at all readily respond is the faradic current. As this stimulus is very much more easily conducted through the skin than is a thermal change many more nerves can be got to respond to it than can be stimulated by cold. If the current used be weak the sensation resulting is a painless fluttering in the distal part of the nerve area. Strong stimulation gives a heavy drawing vibration throughout the whole area which although a sensation of great "bulk" has surprisingly little of the specific quality of pain.

The question whether stimulation of a normal nerve trunk with heat can call forth corresponding sensations in the area of distribution is obviously of considerable interest. It is however by no means easy to decide and we are not in a position to give a definite answer. The most we have obtained has been a very vague sensation of warmth, of all sensations perhaps the most difficult for the subject to be sure of.

The whole matter of the excitability of sensory nerve trunks seems to have escaped the amount of attention it undoubtedly deserves and, considering the simplicity of the necessary procedures, should obtain. We have not been able to give to it any detailed study but have had to content ourselves with demonstrat-

ing that the peculiarities of excitability possessed by a regenerating nerve are merely those of the normal nerve exaggerated to a marked degree[1]).

2. Theoretical Considerations.

In attempting to elucidate the meaning of the various remarkable phenomena which are found in connection with recovery after section of a cutaneous nerve it is as we have already said important to pay particular attention to the facts in their general physiological bearing and not to regard them too exclusively from the purely neural point of view. In our earlier contribution we pointed out that section of a nerve leads to the appearance of certain phenomena which cannot be ascribed to a mere loss or diminution of sensibility however specialised and must be regarded as being other than purely neural manifestations. In the same way it would seem that during recovery there are processes at work other than the mere growth of the new nerve fibres along the connective tissue residue of the degenerated nerve.

The phenomenon of peripheral reference is at once one of the most striking and perplexing features in the process of recovery. In our former paper we were not able to go further by way of interpretation than to suggest that it must depend on some peculiarity of the regenerating nerve. We are now able to shew reason to believe that when a stimulus causes a sensation to be felt not at the point of application but in the area of distribution of the nerve the significance of the reaction is that the nerve fibres themselves have been stimulated. We have shewn that the fibres of a nerve trunk are capable of reacting to the five kinds of stimulus and of yielding sensations of the corresponding specific qualities. This property is difficult to demonstrate in normal nerves for some forms of sensation, those most difficult to elicit being pain and response to mechanical stimulation and heat. The capacity of reacting specifically to all kinds of stimulation is however possessed fully and unequivocally by the regenerating nerve, in regard to which it can be demonstrated under suitable circumstances with great ease and unmistakeable precision. In both cases the sensations are invariably referred to the distribution of the nerve. *These observations shew then that conducting fibres of a peripheral nerve are capable of originating when appropriately stimulated, the five specific sensations*[2]). The sensations thus aroused differ from those originated in the skin in one character only namely localisation. Even in the case of the trunks which have remained abnormally excitable for several years we have found no evidence that nerve fibre stimulation can yield a local sensation. As long as it is felt the sensation is invariably referred to the area of distribution, to the peripheral part of it if the stimulus is moderate, to the whole of it if the stimulation is strong. Now it is obvious that there is a remarkable resemblance between the phenomena of nerve fibre sensibility and those of peripheral reference as found in the recovering area. In the latter

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[1]) One other change noticed in the recovering nerve was a very considerable thickening. Whenever the nerve lay in a part free from subcutaneous fat this change could be observed and the nerve became visible far down into the recovering area.

[2]) The five specific sensations referred to here are course touch, pain, heat, cold and that produced by faradic stimulation. The first and the last are for convenience regarded as distinct though they resemble one another very closely. In the case of the regenerating nerve in fact the referred sensation produced by a weak faradic current and that produced by a firm stroking of the skin are almost indistinguishable.

at an early stage of recovery all sensations are referred and no local response is elicited. With a moderate stimulus the referred sensation is felt at some part of the periphery of the area, when the stimulation is energetic the sensation is felt throughout the area distal to the point stimulated. It may fairly be concluded therefore that the phenomena of peripheral reference are due to something in the nature of nerve fibre stimulation. If this conclusion be justified it leads to the further proposition that *in an area where recovery is in progress the regenerating nerve fibres shew a greatly increased accessibility to direct stimulation.* This increased excitability is such as to yield a characteristic response even in the parts of the area which lie at a distance from the nerve trunk although the response is of course to be obtained in its most impressive form from stimulation applied in the immediate neighbourhood of the nerve.

As recovery proceeds a time arrives when a given spot which previously has yielded peripherally referred sensations only, begins to give a local response. It is difficult to resist the conclusion that the appearance of local sensibility is due to the reestablishment of the connection between nerve fibre and end organ. If this were the case it would be of interest as indicating that the function of the end organ is to do with localisation rather than with acuity. In regard to the function of end organs in general three hypotheses present themselves. First that these structures are concerned with the conversion of specific stimuli into specific nervous impulses, so that for example there would be a series of end organs concerned with deriving from the physical process of heat loss the special sort of nerve impulse which originates sensations of cold. Secondly they may be supposed to be concerned with acuity of sensation, acting so as to magnify or modify the physical processes underlying sensation. Or thirdly as we have suggested they may be mainly or exclusively concerned with the localisation of sensation to the point stimulated. With regard to the first supposition the evidence we have produced as to the specific sensibility of nerve fibres shews that there is no physiological need for end organs to render the physical processes of stimulation capable of originating specific impulses in the nerves. With regard to the second possibility we have found that nerve fibre sensibility is capable of reaching a high grade of sensitiveness. Areas which yield nothing but peripherally referred sensations may come very near the normal threshold of acuity. That they can reach it is difficult or impossible to demonstrate because just as they are approching this degree of sensitiveness local sensibility begins to appear and although the phenomena of reference continue it cannot be proved that the increase of acuity to the normal is not due to the mechanism which endows the part with local sensibility. Nevertheless the evidence derived from the facts of recovery seem to us to point against the view that the end organs, so called, are essentially concerned with sensory acuteness. It does not seem that the relation between the anatomical distribution of end organs and variations in sensibility has been at all accurately established, many parts of the body for example being richly supplied with these structures but possessing sensibility of a very low grade or of a much simplified kind. The case of the cutaneous end organs for touch on hairy parts is somewhat peculiar in that the hairs by their lever action very obviously have a magnifying effect upon the physical disturbance which they transmit to the nerves.

The view that the acquisition of local sensibility is in some way concerned with the relation of nerve fibre and end organ must not be regarded as more than quite tentative. We are aware of many difficulties in the way of accepting it such for example as the presence of end organs where localised sensation is not experienced, e. g. serous cavities. The collateral evidence however of the existence of some mechanism which enables nerve fibre sensibility to be converted into local sensibility is sufficiently strong to lend a certain prima facie plausibility to the suggestion. We shall have occasion to refer later to another possibility as to the function of some of these end organs.

We may now consider what explanations can be offered of the very great increase in accessibility to direct stimulation shewn by the nerve fibres of the re-covering area. Before making the attempt we would emphasise once more the fact that we have to do with an increase of a normal characteristic of nerve fibres rather than with the appearance of a new one. As we have shewn normal nerves possess the same character to a slight extent, regenerating nerves shew it to a more marked extent, while it reaches its fullest development in the recovering area itself. Two principal lines of explanation present themselves. First that the nerve fibres themselves may be in a condition of increased excitability and secondly that they may be physically more accessible to stimulation. In dealing with these possibilities it will be convenient to take into consideration the phenomena of intensification as well as those of peripheral reference. It is clear that there is some close association between the two. They appear together in the early period of recovery, they are both manifested by the regenerating nerve trunk and by the recovering area and they both persist until long after recovery of sensory acuity is complete. As might be expected it is usually easier to demonstrate reference than intensification at a very late period because the demonstration of the latter depends upon a quantita-tive estimation which may be difficult when the abnormality is slight, whereas the former as long as it is present at all is easy to recognise. Intensification it will be remembered may be a character not only of peripherally referred sensations but also of sensations felt locally. It is however most marked in referred sensations and rarely reaches such a degree in local sensations. It also tends to disappear from the latter sooner than it does from the former so that it seems that with the acquisition of locality something has occurred which, while not abolishing intensific-ation tends to allow of its subsidence. Hence it appears probable that intensifi-cation is favoured by the conditions which allow of nerve fibre sensibility or is a direct consequence of that phenomenon. We have seen that the intensified sensation is an exaggerated response to stimulation and does not signify necessarily an in-creased sensitiveness; hence it may be present in a region of hypoaesthesia or in a region of normal acuity. Supposing it to be, as we have shewn reason to suspect, a result of increased nerve fibre excitability it must be due, just as peripheral reference is, either to an abnormal irritability or to an increased accessibility to stimulation.

Anatomical observations upon the results of nerve section and the processes of regeneration confirm the view that the restoration of the nerve is a process which is effected under considerable difficulties and is by no means so simple and inevitable as is perhaps sometimes supposed. It is probable that the fine axis cylinders which grow out from the central end of the nerve are much more numerous than the

axis cylinders originally present before the operation. Whether all this excess of new fibres is retained within the framework of the peripheral end of the nerve is open to question and it is possible that they grow down into the recovering area to some or perhaps to a considerable extent independently of the nerve trunk. If we are to suppose that a recovering area is thus invaded by a large excess of new axis cylinders, a plausible explanation will be available of many of the phenomena of recovery. A great increase in the possibilities of nerve fibre stimulation might for example under such circumstances be expected. Intensification would to a certain extent harmonise well with such an hypothesis. The intensification of a sensation can be estimated quantitatively to a certain extent. This can best be done with thermal sensibility by finding how large an area of normal skin it is necessary to stimulate with a given temperature in order to produce a sensation as intense as that produced by a standard cylinder at the same temperature. In this way it is found that the abnormal sensation is exactly reproduced by stimulation of normal skin, though it may be necessary to make the area stimulated in the latter case several hundred times larger than the abnormal area which yielded the intensified sensation. Such perfect reproduction of intensified sensation cannot be effected by heightening the stimulus applied to the normal, but is possible only by increasing the area stimulated. This observation seems to suggest that intensification means that the stimulus has acted upon a greater amount of nervous tissue than would a stimulus of the same size and strength in the normal. The persistence of intensification and peripheral reference would be accounted for by such an hypothesis, for it might be supposed that the recovering area was at first invaded by a great excess of axis cylinders, only a certain proportion of which could become connected with end organs and furnish the definitive sensibility of the part, while the other axis cylinders remaining unconnected with end organs would gradually atrophy and ultimately disappear, but would as long as any of them persisted endow the part with nerve fibre sensibility, and cause it to shew a slowly diminishing degree of intensification and peripheral reference. The increased accessibility to stimulation of the regenerating nerve trunk is another important phenomenon which would be very readily assimilated by this hypothesis.

Encouraging as is this interpretation of the facts we are not inclined to accept it as being complete. The special difficulty it presents is in regard to the elucidation of peripheral reference and intensification as they occur in response to minutely punctate stimuli as for example pain sensations elicited with a needle. It is very difficult to see how such a stimulus could be regarded as directly exciting such an excess of nervous tissue as would lead to sensations so exaggerated. If then we accept the hypothesis some supplementary mechanism other than that it assumes must be supposed to act. A very obvious suggestion is that during recovery there is an imperfect insulation of the nerve fibres from one another so that an impulse traversing one is communicated to those in its neighbourhood and the corresponding sensation thus magnified. The fact that myelination during regeneration is much slower than the formation of axis cylinders might be taken as confirming this supposition. We are not aware however of any histological evidence pointing to a delay in myelination so great as to correspond with the persistence of intensification and peripheral reference.

A consideration of certain pathological conditions in which irritative nerve lesions are present suggests that a persistent slight irritation of a sensory nerve may give rise to an increased excitability in consequence of which the response of the nerve to stimulation is excessive. The sensation aroused by stimulation of the irritable nerve is more intense and vivid than that aroused by similar stimulation of a normal nerve. The intensity of the response is independent of the sensory acuity of the given nerve, so that the latter may be hypoaesthetic and yet yield sensations of abnormal vividness. This is the condition usually found in cases of irritative nerve lesions. There is however no necessary relation between hypoaesthesia and excessive response. The irritation which causes the excessive response does not in itself affect sensory acuity which may be very low or practically normal. In the latter case the state of affairs is practically indistinguishable from a true hyperaesthesia for a stimulus which barely produces a faint sensation on the normal, produces on the abnormal a sensation of very much greater intensitiy.

In dealing with the question of whether a persistent tendency to irritation of the new fibres in a regenerating nerve area can be regarded as a more or less constant phenomen, it will be necessary to discuss and to attempt to bring into correlation many apparently disconnected facts.

In the consideration of the elementary physiology of the nervous system, a group of facts of fundamental significance has received less attention than its importance should perhaps have attracted. The facts to which we refer are those relating to the mechanisms whereby the nervous tissues are cut off from contact with the general substance of the body. The essential property of nervous protoplasm is its capacity on the one hand to respond to stimulation and on the other hand to yield stimuli. Primitively this capacity may be supposed to be absolutely generalised. In the nervous system as we know it, specialisation has advanced very far and the nervous tissues shew marked predilections to respond to certain stimuli and marked tendencies to react on certain tissues. Nevertheless there is reason to suppose that nervous protoplasm still possesses enough of its original generalised irritability to be affected by contact with tissues in which it is not normally in relation and to react upon such as an irritant. In other words although it has become specialised in such a way as to shew its full activity in response to special circumstances only, it cannot be regarded as ever being absolutely inert when it contact with foreign tissues. Such contacts may totally fail to arouse its specialised activities but they must therefore not be assumed to leave the nervous protoplasm totally unaffected. In other words supposing as the result of an injury a tract of nervous tissue is brought into relation with the connective tissues of the body complex reactions must occur at the point of contact, the tissues will irritate the nerves and the nerves will irritate the tissues. Possibily the irritation of the nerve will not be sufficiently intense to arouse its specialised activity but it will tend to give rise to a constant subminimal excitation. With regard to the effect upon the tissues, the nerve is of course incapable of exciting any of the customary response such as contraction, secretion and so forth, but it will act as an irritating foreign body and produce appropriate changes.

This series of phenomena is seen in its most striking form in connection with the large nerves of the limb which have been divided in an amputation. The out-

growth of new axis cylinders from the cut end produces a marked reaction of the connective tissues into which they grow. This reaction leads to the formation of a mass of fibrous tissue of remarkable density which surrounds and firmly encapsules the irritant which has led to its formation. The bulbous end of a divided nerve and the so called amputation neuroma are to be looked upon then as an expression of the irritating quality of nerve protoplasm and of the fact that this quality is constantly present and not due to the conduction of nervous impulses. At the same time it is clear that the new axis cylinders which are entangled in and encapsuled by the connective tissue of the bulbous end, do not find themselves in an indifferent medium for it is common knowledge that irritative nerve symptoms are very often produced and frequently develop into a serious and highly distressing complication. In such a case we are to suppose that the irritation is sufficiently intense to arouse the specialised activity of the nerve and cause spontaneous pain. In other cases the exaggerated tenderness of the bulbous ends shews that although the irritation is not intense enough by itself to excite actual nervous impulses it leads to the establishment of an irritability which causes the nerve fibres to yield exaggerated responses.

Clinical experience abundantly proves that the division of a sensory nerve is an interference with the equilibrium normally existing between nervous and connective tissues which carries with it the danger that in any given case prolonged or even permanent disturbance may ensue. Even when immediate suture of a nerve is performed a similar though less risk is incurred. Most clinicians of any experience must have seen cases in which, in spite of restoration of function having taken place to a considerable extent, the patient's life has been made a burden by the irritative symptoms which have developed.

That the insulation of nervous tissues from contact with others which are capable of irritating or being irritated by them is of great physiological importance is shewn by many facts in the structure of the nervous system and serves to explain certain anatomical features which are otherwise obscure. The elaborate investment of the cerebro-spinal axis in a series of specialised membranes and its isolation in a fluid of a highly specialised kind have generally been explained as mechanisms developed to protect the nervous structures from gross mechanical injury. When these arrangements are carefully considered the most striking character they possess, in addition to being protective in the ordinary sense, is the completeness with which they seclude the central nervous system from contact with the connective tissues of the body in general.

It is not necessary here for us to enter upon a detailed examination of the numerous anatomical facts bearing upon this matter. Before passing on however to those aspects of it which especially concern us, one other peculiarity of more general interest may be mentioned. It cannot be regarded as without physiological significance that in the structure of the central nervous system the ordinary connective issue of the body plays so very small and unimportant a part, while the skeletal properties which are peculiarly necessary in the brain and spinal cord are supplied by a special tissue closely related in origin with the actual nervous elements. It would seem that the neuroglial material owes its great development not merely, and perhaps even not chiefly, to its being mechanically successful

as a supporting tissue but also to its being, unlike all the mesoblastic tissues of the body, physiologically inert towards nerve protoplasm. The peripheral nerves from the very nature of their function cannot be protected from contacts which would produce reaction by a general seclusion such as is satisfactory in the case of the central nervous system. Each individual fibre therefore must be protected and restrained by a special envelope which need not be present around fibres contained in the central nervous system. The neurilemma seems to fulfil these requirements. It is absent or rudimentary in the brain and spinal cord where the nerve fibre can meet only such tissues as are physiologically inert, but it is present everywhere else. Provided with this sheath a nerve fibre can traverse any part of the body and remain inert to all the tissues with which it comes in contact except the end organ with which it is functionally related.

When a nerve trunk is divided and sutured, however carefully, there can be little doubt that the regenerating axis cylinders, which are more numerous than those of the normal nerve, cannot all of them reach and be contained within the neurilemma sheaths of the peripheral end. Some of them, probably even a large number, invade the tissues about the nerve trunk and meeting with material no longer physiologically inert tend to pass into a condition of abnormal irritability. Possibly, even supposing all the new axis cylinders could be conducted to the original neurilemma tubes of the peripheral end, they would still be subject to a certain irritation seeing that these sheaths undergo remarkable and well known changes after a nerve is cut. This neurilemma proliferation fills the sheath with a more or less cellular material through which the new fibre has to make its way. That this new tissue is as inert towards the axis cylinder as the normal nerve sheath seems doubtful, and the facts suggest that some time must elapse before physiological equilibrium is reestablished.

The above are the principal considerations which lead us to infer that an excessive irritability is aroused in nerve fibres which are undergoing regeneration. Certain further collateral evidence might be adduced in support of this conclusion but we do not propose to enter upon it here. We may however bring together one or two facts of a certain corroborative value in relation to the antagonism between nervous tissues and those of the body generally which we regard as of fundamental significance in physiology.

While the connective tissues act in such a way as to resist and restrain invasion by axis cylinder processes, these very antagonistic changes appear to exercise a stimulating effect upon the growth of the nerve substance. It is a familiar fact that an amputation neuroma contains a great length of convoluted and tortuous axis cylinders. The stimulus to this excessive growth and equally of course to the growth which accompanies regeneration has been generally assumed to come solely from the nerve cell of which the axis cylinder is a process. This supposition has left unexplained the striking fact that no regeneration occurs within the nervous system. It has been thought that the relative absence there of the neurilemma sheath is connected with this incapacity. The difficulty in enforcing this association seems to be that it cannot be shewn that the presence of a neurilemma sheath is essential to the sprouting of the cut axis cylinders which is the beginning of regeneration, for such sprouting occurs no less in an amputation stump than in a sutured

nerve. Supposing however the stimulus to regeneration be regarded as coming from the contact of the cut axis cylinders with extra-neural tissues, the absence of restoration after section of the cord would be explained while the significance of the presence of the neurilemma in one situation and not in the other would also be elucidated.

We have already touched upon some of the difficulties in making out the significance of the sensory end organs in the skin and have pointed out that no satisfactory generalisation has been made which brings their structure and distribution into relation with the sensory acuity of the skin. We do not propose to enter upon any further extended discussion of this very complicated matter here but would call attention to certain very obvious facts in the structure of these end organs. In the great majority of all their numerous forms, the encapsulation of the organ in a more or less structureless sheath of considerable thickness is a well marked feature. Contained within this sheath is a naked nerve filament which is usually much convoluted. The frequency of this arrangement suggests that the protection of the bare nerve fibre from contact with tissues not physiologically indifferent to it is an important part of the function of the end organ. It is generally accepted that these encapsuled organs are concerned with sensations other than those of pain, while fibres which end in free ramification swithout encapsulation are regarded as having to do with pain sensations. If this distinction could be accepted as a fact some light might possibly be thrown upon the nature of pain sensibility, the naked ramifications of the pain fibres being regarded as kept in a condition of excitability slightly in excess of the other nerve terminations, and pain being looked upon as a sensation normally "intensified"[1]).

The physiology of sensibility to pain presents many extremely difficult problems especially in regard to the nature of the peripheral mechanism. In the other forms of sensibility the nervous impulse which arouses the sensation is initiated by a single simple physical process whereas in the case of pain the nervous impulse may be aroused by any one of a number of heterogeneous processes of thermal, chemical, mechanical or electrical nature. The common feature presented by these is that they are capable of damaging the tissues to which they are applied. Little if any light however is thrown upon the intimate nature of the stimulus by this fact seeing

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[1]) From the foregoing and what we have said earlier it will be seen that two suggestions are put forward as to the significance of the sensory end organs of the skin, one being that they are concerned with the localisation of sensation and the other that they serve to insulate the terminal nerve twigs from contact with the non-neural tissues of the body. The two views are at first sight incompatible with one another for if the naked nerve ramifications are the terminal structures concerned with pain sensations and get their special capacity from the absence of encapsulation according to the second suggestion, it would follow according to the first suggestion that pain sensations are not localisable. The difficulty is a serious one; certain considerations however suggest themselves as possibily rendering it not altogether insurmountable. In the first place opportunities for testing the localisation of sensations of mere pain unmixed with any other sensation are not such as to allow any very positive statement to be made as to the normal extent of this capacity; secondly sensations of pain being habitually accompanied by an almost immediate motor response the localisation of them is aided by this accessory mechanism; finally in parts of the body (serous cavities) where pain is the only form of sensibility, pain when experienced (e. g. in disease) is characteristically vague and diffuse however intense it may be.

that the characteristic sensation is almost always produced by a strength of stimulus of such a low grade that any actual injury can scarcely be conceived to have been inflicted. Moreover experience in testing sensibility to pain shews that a very little actual injury inflicted upon a pain spot destroys its sensitiveness. We must suppose therefore that in all ordinary testing with stimuli of about the normal threshold strength no more real damage is done to the tissues than in testing any other form of sensibility. Thus the characteristic feature of pain sensibility is so to say the *disproportion* between the stimulus and the response, for the function to be served is the anticipation of injury rather than the notification of it. It is difficult to see how a requirement such as this and differing so much from the conditions necessary for other forms of sensibility, could be satisfied unless the nervous tissue concerned is in a state of especially heightened excitability. That heightened excitability can be established and that it leads to the very disproportion between stimulus and response which seems to be demanded for the normal mechanism of pain sensibility, is abundantly proved by the facts of intensification in a recovering area. The suggestion that the essential mechanism in pain sensibility is the permanent excessive excitability of the nerve filaments which subserve it, is possibly to some extent borne out by the well known instability of this form of sensibility and the fact that it is liable to disorder to a far greater extent than any other. In considering the views which are expressed here it will naturally be asked whether there is any direct evidence that the peripheral pain mechanism is more readily excitable than the other mechanisms. As it happens this question has already been dealt with from another aspect by *von Frey*. In his classical researches upon the sensibility of the skin he shewed that since touch spots and pain spots could be excited by similar stimuli, their thresholds could be compared. He found that when a mechanical stimulus was used the pressure needed to excite pain sensations from the pain spots was higher than that needed to excite touch sensations from the touch spots. That is to say the threshold for pain is higher than that for touch, a result which might be expected from a consideration of general principles. With punctate stimulation with the faradic current he found however a striking difference in that the pain threshold was lower than the touch threshold. Moreover he found evidence strongly suggesting that with this form of stimulus it was the terminal nerve fibre rather than the end organ that received the stimulation and originated the response. These observations seem to shew that faradic stimulation furnishes a means of comparing directly the excitability of two groups of nerve fibres, for it allows the influence of the end organ to be excluded. Tested in this way then the pain nerve fibres are found to be more readily excitable than the touch nerve fibres. Thus these observations of *von Frey* furnish direct evidence of the excess of excitability which we have given other reasons for supposing to be a normal feature of the pain mechanism and possibly an explanation of some of its perplexing characteristics.

In attempting to shew the importance of the reactions which arise when nervous tissue is brought into direct contact with the extraneural connective tissues of the body we have spoken as if such disturbances of what may be called neurosomatic equilibrium were always of traumatic origin. That such conditions may arise apart from injury is shewn in the various forms of connective tissue over-

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growth of neural origin which when multiple and wide spread are referred to as *Recklinghausen's* disease or diffuse neuro-fibromatosis. Such conditions shew the manifestations which may be expected to ensue when there is a breach in the isolation of nerve fibres from the other tissues; namely connective tissue overgrowth on the one hand and increased irritability of the affected nerves on the other.

The foregoing discussion has been almost necessarily somewhat diffuse and it is therefore desirable that we should resume in summary form the principal considerations put forward in it.

Normal sensory nerves when stimulated in the part of their course proximal to their areas of distribution yield corresponding sensations when subjected to certain specific stimuli especially cold and the faradic current (specific excitability of nerve fibres). The fact that they do not respond unmistakeably to all the primary stimuli is probably due not so much to insusceptibility as to inaccessibility to stimulation.

The sensations aroused by nerve fibre stimulation are of normal characters except in regard to localisation. They are felt not at the point stimulated but in the area of distribution of the nerve — in the peripheral part of the area if the stimulus is moderate, throughout the area if the stimulus is energetic.

During regeneration of a sensory nerve the regenerating part shews a great increase in the specific excitability of its fibres. The primary stimuli (touch, pain, heat, cold and the faradic current) readily arouse corresponding sensations.

The sensations aroused by nerve fibre stimulation of regenerating nerves are of characteristic quality corresponding with the stimulus and have precisely the same peculiarities of localisation as have sensations due to nerve fibre stimulation of normal nerves.

Peripheral reference in the recovering area itself at an early stage reproduces all the characters of nerve fibre stimulation as regards localisation, viz absence of sensation at the spot stimulated, localisation of sensation to the periphery of the area if the stimulus is moderate, and diffusion of the sensation throughout the area if the stimulus is energetic.

It is therefore highly probable that peripheral reference is due to nerve fibre stimulation and that in the recovering area the regenerating nerve fibres are abnormally accessible to stimulation.

It is suggested that the restoration of true local sensibility may be due to the re-establishment of the connection between nerve fibre and end organ.

In view of the fact that the reappearance of true local sensibility does not abolish reference, and the fact that the latter persists for a very long period and disappears gradually it is suggested that in the recovering area there is an excess of new axis cylinders over the number normal to the part. This view is held to be confirmed by the histological facts of regeneration.

Intensification of sensation in the recovering area is characteristic of all sensations whether they are elicited by a threshold stimulus above, at or below the normal.

It is therefore concluded that intensification is a phenomenon altogether distinct from and independent of sensory acuity.

Pathological evidence tends to shew that excessive reponse to stimuli is an indication of persistent slight irritation of the nerve. It is therefore suggested that the intensification of sensation elicited from the recovering area is due to the regenerating nerve fibres being subject to chronic irritation.

The source of this irritation is found in the contact of the new nervous tissue with the non-nervous tissues of the part and the consequent reactions set up.

It is pointed out that the insulation of nervous tissue from non-nervous is very elaborately provided for in the anatomy of the normal nervous system and is probably therfore of essential importance. The neurilemma and the end organ of the peripheral sensory nerve are regarded as having important insulatory functions. It is suggested that if the free terminal ramifications of sensory nerves are the end organs subserving pain sensibility, the specific quality of the sensations resulting from stimulation of them may be due to a slight normal irritation consequent on incomplete insulation. The suggestion is strengthened by the observation of *von Frey* that for faradic stimulation the pain threshold of the skin is lower than the touch threshold.

In conclusion we may add that the general purpose of this paper is an attempt to shew that the peculiarities of function displayed by a cutaneous area during the recovery of sensibility, strange in many ways as they are, are not altogether isolated phenomena but can be brought into correlation with many well known facts in the anatomy and physiology of the nervous system and in its modes of reaction to injury and disease.

Description of Figures.

Figs. 1 to 4. Recovery in area of Left Saphenous nerve. The nerve was divided at the level of the knee joint. The illustrations embody the results of detailed examination 11 months after the operation.

In each case the *broken outline* is the outermost limit of change of any kind which followed the nerve section, and the *continuous line* shews the area anaesthetic to touches with cotton wool or the camel's hair brush at the time of examination.

Fig. 1. **Sensibilty to touch**, tested with *von Frey* hairs.

Dots. Touch spots which reacted to hair of 70 mgr pressure (normal threshold).

Steres. Touch spots which reacted to hair of 140 mgr pressure.

Crones. Touch spots which reacted to hair of 800 mgr pressure.

Circles. Touch spots which reacted to hair of 3480 mgr. Peripheral Reference not indicated.

Fig. 2. **Sensibility to pain**, tested with authors' algometer at pressure of 2240 mgr. The dotted area is that within which the phenomena of Intensification and Peripheral Reference were obtained. All the referred sensations were felt within the lower end of the area enclosed by the continous line.

Fig. 3. **Sensibility to heat.** The dots indicate the places which yielded the sensation hot when touched with a copper cylinder with a contact surface 1 mm in diameter at a temperature of 50° C.

Fig. 4. **Sensibility to cold.** The spots marked are those which yielded the sensation cold when touched with a copper cylinder with a contact surface 1 mm in diameter at a temperature 0° C.

Dots indicate places which yielded sensations of cold felt locally.

Crones indicate places which yielded sensations of cold felt peripherally.

Circles indicate places which yielded sensations of cold felt locally and peripherally.

Figs. 5 and 6. Middle Cutaneous nerve of Right Thigh.

Sensibility to cold. The spots marked are those which yielded the sensation cold when touched with a copper cylinder with a contact surface 1 mm in diameter at a temperature of 0° C.

Dots indicate places which yielded sensations of cold felt locally.

Crones indicate places which yielded sensations of cold felt peripherally.

Circles indicate places which yielded sensations of cold felt locally and peripherally.

Fig. 5. $3^1{}_2$ months after section of nerve shewing the condition immediately before the beginning of recovery. The fringe of normal cold spots has been marked out immediately around the area of thermoanaesthesia.

Fig. 6. 6 months after section of nerve. Recovery of sensibility to cold well marked.

Fig. 7. The Distribution of proximal and peripheral reference. Internal cutanueou of left forearm. Recovery well advanced. Area tested with cylinders at a temperature of 0° C.

Each area indicates a spot the stimulation of which yielded a referred sensation of cold.

The direction of the arrow indicates the direction of the reference. Double arrows mark spots which yielded peripheral and proximal reference. The lines shew the position of the incisions through which the three branches of the nerve were divided.
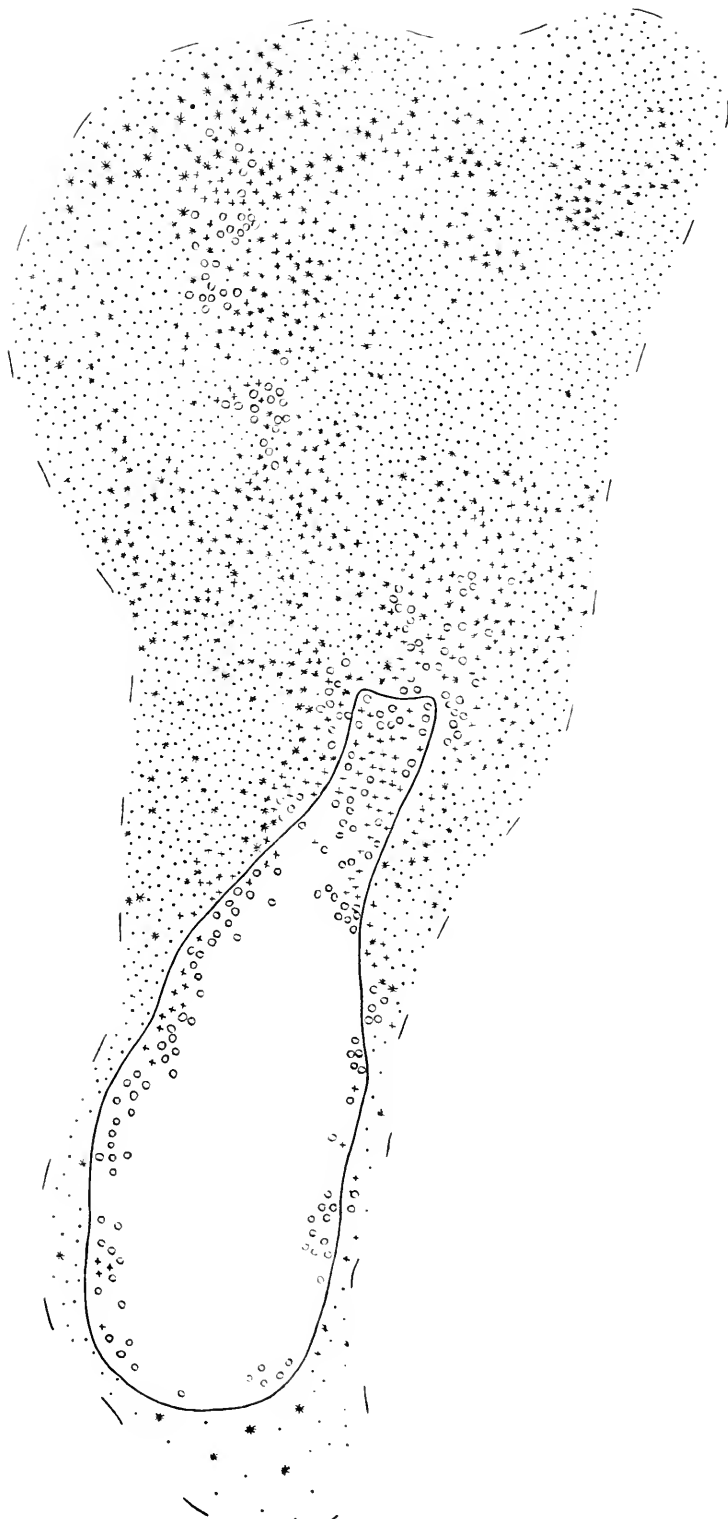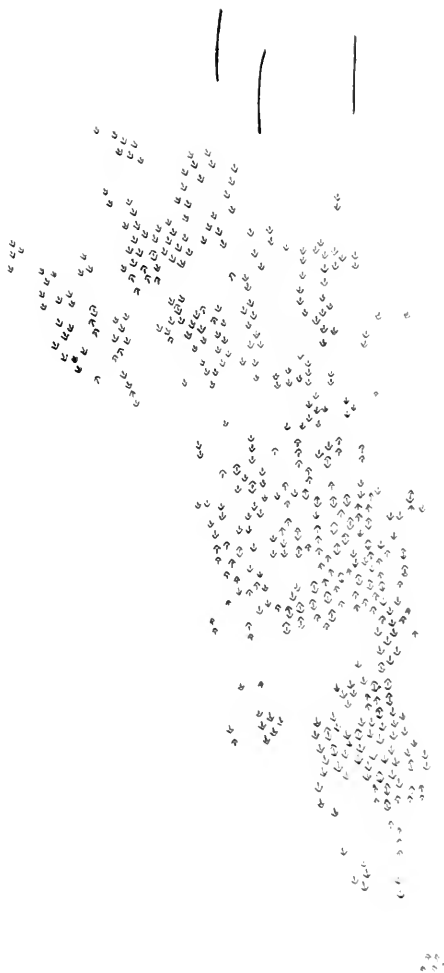
Fig. 1
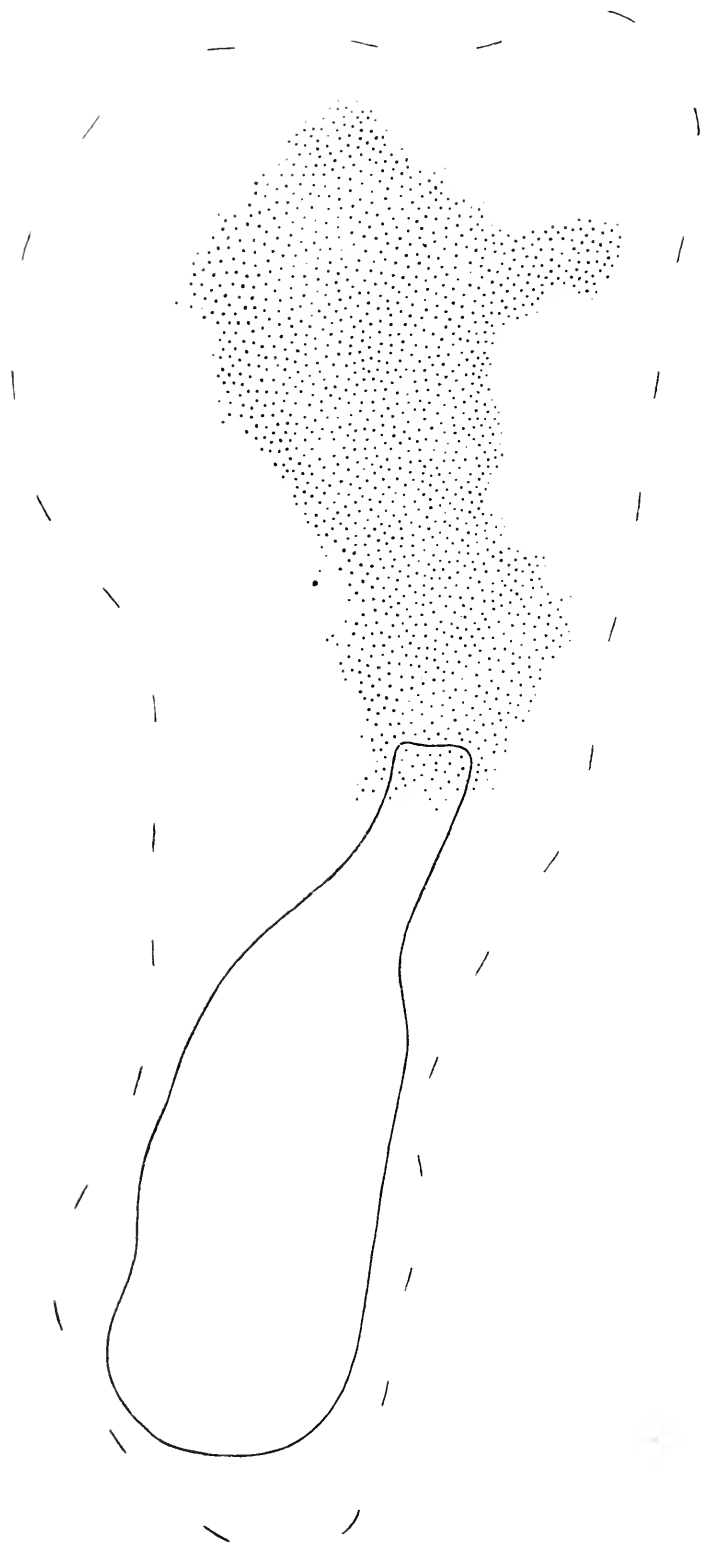
Fig. 2.

Fig. 3.
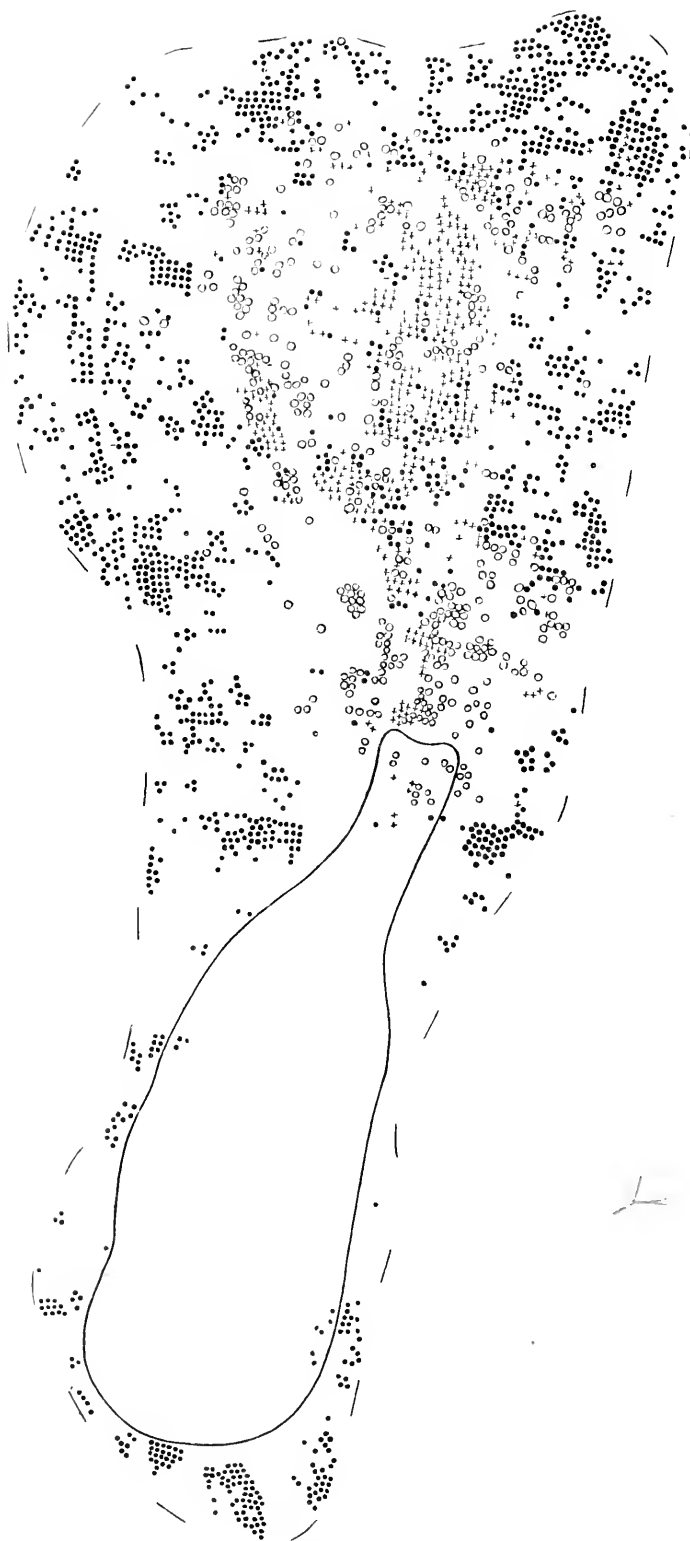
Fig 4.

Fig. 5.

Fig. 6.

Fig. 7.

Resumé.[1]

1. Unmittelbar, bevor sich die ersten Anzeichen der Wiederherstellung zeigen, weist ein seiner Nervenversorgung beraubter Hautbezirk eine zentrale Region auf, wo alle Arten der Hautsensibilität verloren sind und sie umgebend eine Zone, in welcher alle Arten der Hautsensibilität in ihrer Schärfe herabgesetzt sind. Die Qualität der Empfindungen, die da hervorgerufen werden können, ist in keiner Weise abnormal.

2. Alle Arten der Sensibilität haben die Tendenz, gleichzeitig wieder zu erscheinen, ausgenommen die Empfindung für Temperaturen höher als die Hautwärme, welche etwas später auftritt. Diese Verzögerung ist wahrscheinlich zum Teil wenigstens durch die Schwierigkeit zu erklären, welche es macht, die Wärmeempfindung in ihrer hypoästhetischen Form nachzuweisen.

3. Jede wiederkehrende Sensibilität ist zuerst hypoästhetisch.

4. Jede wiederkehrende Sensibilität zeigt das Phänomen der Intensifikation und der peripheren Verschiebung.

5. Intensifikation und die periphere Verschiebung haben keine Beziehung zur Hypoästhesie und persistieren lange, wenn die volle Schärfe der Sensibilität schon wieder hergestellt ist.

Die Untersuchungen, auf welche sich diese Schlußfolgerungen stützen, hatten die experimentelle Durchschneidung von sieben Hautnerven von verschiedener Stärke und in verschiedenen Körperregionen zur Grundlage, die bei dem einen oder dem andern der Autoren ausgeführt wurden. Der größte durchtrennte Nerv versorgte einen Bezirk von 280 Quadratzentimetern.

Heads Beobachtungen.

Nach Head hat die Durchtrennung eines Nerven zur Folge, daß ein zentraler Bezirk mit Verlust aller Arten von Hautsensibilität auftritt — umgeben von einer Zone, die mit einer eigenartigen und besonderen Form von Sensibilität ausgestattet ist. Diese Sensibilität liefert Empfindungen auf Schmerzreize, auf extreme Temperaturen, aber nicht auf taktile Reize.

Die von dieser Zone gelieferten Schmerzempfindungen sind ganz besonders unangenehm.

Wenn die Wiederherstellung eintritt, erscheint die Sensibilität für Schmerz und extreme Temperaturen zuerst ohne Tastsensibilität. Die Schmerzempfindungen sind abnorm unangenehm, die Wärmeempfindungen abnorm intensiv und beide haben die Tendenz auf distale Partien bezogen zu werden. Die Sensibilität für Berührungen und für mittlere Temperaturen tritt erst später wieder auf.

Gleichzeitig mit ihrem Auftreten verschwindet die Intensifikation von Schmerz und Temperaturempfindungen und die distale Verschiebung. Diese Phänomene werden durch die Hypothese erklärt, daß es zwei verschiedene Arten von Nervenfasern gibt, von denen die eine der Empfindung für Schmerz und extreme Temperaturen (protopathische) dient und zu einem früheren Zeitpunkt regeneriert, und eine andere, welche die Sensibilität für Berührung und mittlere Temperaturen trägt und erst später regeneriert (epikritische).

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[1] This resumè is an abstract of the paper actually read at the Congress & therefore includos no summary of the chapter here published which deals with the physiological interpretation of Intensification & Peripheral Reference.

Die Beobachtungen, auf welche Heads Schlüsse aufgebaut sind, wurden nur an einem einzigen Hautbezirk von fehlender Sensibilität gemacht, der experimentell auf der Haut des Vorderarms erzeugt war.

Heads Arbeit wird also sowohl bezüglich des von ihm gegebenen tatsächlichen Befundes als auch der daraus abgeleiteten Schlußfolgerung einer Revision unterzogen.

Wir zeigen, daß in keinem von unseren wiederholten Versuchen die Verzögerung im Wiedererscheinen der Tastempfindung zu finden war, welche Head beschreibt und die seine Hypothese verlangt.

Die Erklärung dafür, daß er nicht das Wiederauftreten der taktilen Sensibilität gleichzeitig mit dem der Sensibilität für Schmerz und Wärmereize beobachtete, ist darin zu suchen, daß die erstgenannte Sensibilität zuerst in einer auffallend hypoästhetischen Form auftritt.

Man muß der Tatsache Beachtung schenken, daß die Abart der thermischen Sensibilität, die er protopathische nennt, nur eine Thermohypoästhesie darstellt, eher als eine getrennte und spezifische Art von Sensibilität.

Bei keinem der von den Autoren angestellten Versuche konnte konstatiert werden, daß mit dem Wiedererscheinen der normalen taktilen Sensibilität das Verschwinden der Intensifikation und der peripheren Verschiebung auftrat, was nach Heads Hypothese dann platzgreifen mußte.

Außerdem ergaben sich noch zahlreiche andere Diskrepanzen zwischen Heads Resultaten und denen der Autoren. Es ist anzunehmen, daß mindestens ein Teil davon durch die begrenzten Möglichkeiten von Revision oder Bestätigung bedingt sind, die Head bei seinem einem Experiment zu Gebote standen, auf das er seine Untersuchungen beschränkte.

Betrachtungen über den speziellen Charakter der Sensibilität in regenerierenden Hautbezirken.

Es kann gezeigt werden, daß bestimmte Eigentümlichkeiten der Sensibilität zum erstenmal dann auftreten, wenn die Wiederherstellung einsetzt und daß sie ganz spezifisch für den Prozeß der Regeneration sind — da sich nichts, was ihnen irgendwie gleichen würde, in dem affizierten Bezirk in dem Zeitpunkt findet, der unmittelbar den ersten Anzeichen der Funktionswiederherstellung vorangeht.

Von diesen Eigentümlichkeiten sind die wichtigsten, die Intensifikation und die periphere Verschiebung.

Deshalb und aus gewissen anderen Gründen können diese Erscheinungen nicht als Stadien in dem fortschreitenden Prozeß der Regeneration angesehen werden, sondern sie müssen als dazutretende Erscheinungen aufgefaßt werden und als akzidentelle, was die tatsächliche Wiederherstellung der Funktion angeht.

Es ist wahrscheinlich zu machen, daß sie in Wesen beruhen und zusammenhängen mit einem Zustand abnormaler Irritabilität der regenerierenden Nervenfasern. Es wird gezeigt, daß wahrscheinlich ein konstanter leichter Reizzustand der Nervenfasern dazu tendiert, eine übertriebene Reaktion auf einen wirksamen Reiz zu verursachen, aber nicht notwendig eine vermehrte Reizbarkeit oder eine wirkliche Hyperästhesie.

Dieser Standpunkt stimmt überein mit dem bekannten Fehlen einer Beziehung zwischen sensorischer Schärfe und der diskutierten Erscheinung.

Unter Intensifikation wird jene Eigenschaft wieder erwachender Sensibilität verstanden, auf Reiz eine abnorm intensive Antwort zu geben, z. B. so daß Schmerzempfindungen ungewöhnlich unangenehm, kalte Empfindungen übertrieben lebhaft sind.

Unter peripherer Verschiebung ist die Tendenz aller von einem regenerierenden Bezirk aus erregten Empfindungen zu verstehen, in dessen distalen Partien empfunden zu werden — entweder allein wie in den ersten Stadien oder zusammen mit einer Empfindung an dem Ort des Reizes.

Diese Phänomene ändern sich nicht gleichermaßen mit der Schärfe der Sensibilität. Sie können Empfindungen begleiten, die von einem noch ausgesprochen hypoästhetischen Bezirk aus ausgelöst werden oder von einem Bezirk mit normaler Schärfe der Sensibilität.

The Hunterian Lectures

ON

THE PRINCIPLES AND TECHNIQUE OF

THE OPERATIVE TREATMENT OF MALIGNANT DISEASE OF THE MOUTH AND PHARYNX

Delivered before the Royal College of Surgeons of England on March 3 and 5, 1913

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The Hunterian Lectures

ON THE

PRINCIPLES AND TECHNIQUE OF THE

OPERATIVE TREATMENT OF MALIGNANT DISEASE OF THE MOUTH AND PHARYNX.

LECTURE I.

Delivered on March 3rd.

MR. PRESIDENT AND GENTLEMEN,—The respects in which the surgery of cancer of the mouth and pharynx falls below the standard that has been reached in many other departments of the art may be classified in three groups. First and most important is the uncertainty of cure ; secondly, the danger of the operation and the distresses of the convalescence ; and thirdly, the mutilation and disability which may be left by an operation otherwise perfectly successful.

THE UNCERTAINTY OF CURE.

There can be no doubt that this is the great stumbling-block of surgeon and patient alike. It prevents the latter seeking advice in the earliest stages of his malady because he usually suspects its nature and is probably possessed of the deeply rooted conviction that cancer is incurable, while the former is discouraged from the hopeful and enterprising attitude which alone can lead to progress. He is aware that

in any but the earliest cases he may submit his patient to a dangerous operation and a distressing convalescence, only to leave him still a victim to the disease the course of which will, perhaps, not even have been mitigated. This consideration applies, no doubt, to all operations for malignant disease, but is of particular force in regard to malignant disease of the mouth and pharynx. Here, when recurrence after operation takes place, it usually does so within a few months, so that the patient has not even secured from the treatment a moderate interval of comfort and good health.

This liability to early recurrence has, however, one less gloomy aspect, and that is, that should the patient remain well for a relatively short time he may be assured that the chance that permanent cure has been effected is very great. Many authorities seem to be of opinion that a year's freedom from recurrence is good evidence of cure in the case of squamous epithelioma. I have myself seen only one case in which a true recurrence occurred after a longer interval, and would venture the opinion that if at the end of 12 months from the operation the most careful examination fails to show any suspicion of disease, a very favourable prognosis may be given. Such a decision must, however, be founded on very careful examination, and needs a certain amount of experience to give it much value. For the purpose of considering the results of treatment in general it is, I think, desirable to double the period of probation, and not to regard cases as cured with any certainty until two years have elapsed. In these remarks I am, of course, leaving out of account cases of a second outbreak of the disease, such as will occur, for example, in a distinct part of a leucoplakic tongue many years after a growth has been removed.

An early superficial carcinoma on the free part of the tongue, if treated with due regard to modern principles, should be, and is, curable in practically all cases. The principles, through the application of which such results can be obtained, we owe to the late Sir Henry Butlin. His formulation of the two-stage operation, his insistence upon a systematic gland dissection in every case, and his work in the advancement of early diagnosis have incalculably enlarged the resources of surgery, and have furnished other

workers in the field of his enthusiastic labours with a rich endowment of hope.

When, however, we turn to the more advanced cases and to growths in less easily accessible regions, we find the extent to which we can expect cure in any given case is very greatly reduced. It is just in these cases that a reasonable prospect of success would be of the greatest value. I am very far from suggesting that there should be any relaxation in our efforts to secure early diagnosis, but I am inclined to think that until we can attain at least fairly good results in the moderately advanced cases—that is to say, the average cases—it will be difficult to get the public to appreciate the great advantages of early diagnosis. The general conviction of the incurability of cancer is founded on the results of operation in the average fairly advanced case, and until this conviction is shaken I fear the public will remain relatively indifferent and pessimistic as to the advantages of early treatment. Every surgeon of any experience is aware that as regards its accessibility to treatment early cancer is a totally different disease from even moderately advanced cancer, but I am very doubtful as to whether we shall ever be able to enforce this fact by direct statement so long as the treatment of advanced cases furnishes the public with so many terrible object lessons in the apparent intractability of the disease.

VARIETIES OF MALIGNANT DISEASE MET WITH IN THE MOUTH AND PHARYNX.

In inquiring into the difficulties of eradicating malignant disease of the mouth and pharynx, the first step is to analyse as far as possible the varieties in which the disease occurs. The clinical and pathological study of this part of the subject does not seem to have been followed out as fully as it might have been, and I believe it is not generally appreciated how regularly the disease tends to follow certain types and to infest certain regions, and how much information for the guidance of treatment and prognosis can be got from a familiarity with these characteristics.

ANATOMICAL VARIETIES.

The Mouth.

The distribution of malignant disease within the mouth is so familiar that no detailed description is necessary. Four cardinal types are recognisable :—

(*a*) Growths of the oral part of the tongue—that is, of the part of the tongue which lies in front of the circumvallate papillæ and is clothed on its dorsum and margins with papillary mucous membrane. Usually the tumour begins on the lateral margin, frequently on the dorsum, and sometimes on the under surface.

(*b*) Growths of the floor of the mouth. These begin either on the sublingual fold between the tongue and the molar teeth or on the frænum of the tongue. A distinct difference in the malignancy of the two forms is frequently to be observed.

(*c*) Growths of the gum starting in the mucous membrane around the teeth. This form may cause difficulties of diagnosis. The bone is involved early. In the lower jaw it may merely be exposed by the growth ; in the upper jaw the bone being much less dense is apt to undergo rapid destruction, with perforation of the antrum. Very often in these cases the direct evidence of the presence of malignant disease is slight and ambiguous.

(*d*) Growths of the cheek are the least common. They usually start somewhat outside the angle of the mouth. The closure of the jaws and the suppuration in the cheek may cause the diagnosis of an inflammatory lesion to be made.

The Pharynx.

It is in regard to this group that the recognition of the different anatomical types is most important. Early diagnosis and satisfactory treatment may depend entirely upon the identification of the exact form of the disease, and it frequently happens that such identification is by no means easy unless it is founded on considerable experience. The growths of the pharynx seem to have been but little described and classified from the point of view of their starting-points. Post-mortem evidence is, of course, valueless, since death does not usually occur until the growth has spread widely. Clinical evidence obtained by examination by the laryngoscope or by the direct method has frequently proved in my experience to be most misleading. The only means which can give exact information is the direct observation of these tumours in their early stages at operations undertaken for their removal. No very valuable statements can be made, therefore, until our experience derived from this source is much larger. I shall, therefore, give merely a provisional classification based on my own operative experience. I may add, with regard to methods of examination, that I attach far more importance to palpation with the finger than to any other method. As far down as the upper opening of the larynx it is a source of information superior to any other. External examination of the neck, as we shall see later, is sometimes of great value in the diagnosis of the primary tumour, and occasionally is all that is necessary. Finally, I would remind you of the fact, familiar to all, that almost invariably at operation the growth is found to be more extensive than was expected, and sometimes very much more extensive.

Tumours of the pharynx lend themselves readily to classification into fairly definite groups. The various groups which can be distinguished are of great practical importance, since for each of them a standard operation can be devised which gives adequate means of dealing with any operable tumour of the given group. The differentiation is not.

however, merely anatomical, but corresponds also fairly accurately with certain peculiarities of age and sex incidence.

Seeing that adequate exposure of a given tumour is an essential preliminary to satisfactory removal of it, it is obviously of great importance for the surgeon to recognise the class to which the tumour belongs and thus to be able to choose the proper method of attacking it, for an unsuitable method of approach may render impossible the satisfactory completion of the highly complex operation which is often desirable.

The anatomical classification which I have found most convenient is as follows : (1) nasopharyngeal tumours ; (2) oropharyngeal tumours ; (3) epilaryngeal tumours ; (4) tumours of the sinus pyriformis ; and (5) hypopharyngeal tumours. (Fig. 1.) Each of these groups must be dealt with by a special operation, whereby any member of the group can be exposed and if operable removed.

1. *Tumours of the nasopharynx.*—This group is peculiar in two important particulars : first, in that the squamous epithelioma is almost entirely absent from it ; and secondly, because symptoms are often very inconspicuous in the early stages, so that it is almost impossible for a diagnosis to be made at a period when successful treatment is possible. In my experience almost all true malignant tumours here are endotheliomata of a peculiar and characteristic type. A sarcoma is occasionally found. All these occur on the roof and lateral wall, especially the latter.

The symptoms may be divided into three groups.

(*a*) *Pharyngeal.* Hæmorrhage, obstruction of the nose. Both these are much less common than is sometimes thought, and this is perhaps a reason why a diagnosis is often not made.

(*b*) *Symptoms due to direct extension of growth.* Into the lateral wall, causing unilateral fixation of soft palate, deafness from pressure on Eustachian tube, trigeminal neuralgia through involvement of inferior maxillary nerve and sometimes superior maxillary nerve, closure of

FIG. 1.
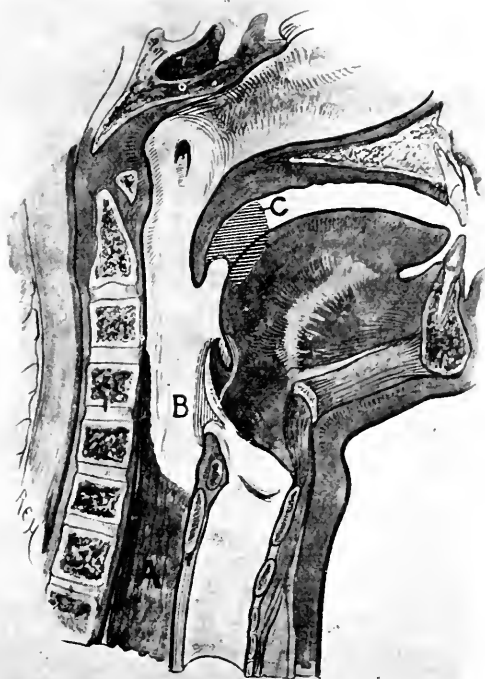
Diagrammatic section of pharynx to show situation of three
of the principal regions in which tumours mainly occur.
A, Hypopharyngeal group.   B, Epilaryngeal group.
C, Oropharyngeal group.

jaws through extension to internal pterygoid muscle. Into the skull through the basal foramina, causing symptoms of cerebral tumour. This latter mode of extension is relatively late, the former relatively early.

(c) *Enlargement of glands.* This occurs early, and on account of the relative absence of nasopharyngeal symptoms is apt to cause difficulty. The glands are characteristic clinically. They are firm but accompanied by much periadenitis, so that they are frequently mistaken for glands of inflammatory origin. One of my patients had been treated with tuberculin for six months before I saw him. As a matter of fact, the condition clinically does closely resemble the fibrotic variety of tuberculous glands and to some extent gummatous glands.

The endothelioma of the pharynx is a remarkable and interesting tumour, presenting many very characteristic features which have not, however, received much attention on account probably of cases not having been operated on very frequently. I shall not be able to deal with these tumours fully here, but may mention their especial frequency in the young adult and adult male, the liability to show inflammatory signs and to suffer inflammatory complications such as recurrent suppuration, and their extreme intractability to operative treatment in any but the very earliest stages. The area in which they occur does not exactly correspond with the anatomical classification I have given, as in addition to the lateral wall of the nasopharynx and to some extent the roof, they originate in the tonsil not very uncommonly. It is perhaps worthy of note that the tract of tissue about the inner ends of the two first visceral clefts is that to which this very special class of tumour is practically limited.

I have known of cases in which such a tumour has been found in a tonsil which has been removed by enucleation and in which no recurrence has occurred. The more fully developed cases with which alone I have had to deal have proved quite inveterate. The disease can be checked for a time but not cured. In all these cases, however, the diagnosis might have been made very much earlier had the

special features of the disease been more generally known. In regard, therefore, to endothelioma of the nasopharynx and tonsil (pharyngeal endothelioma) we are at present entirely dependent upon very early diagnosis, and until that is generally mastered the surgeon will remain unable to give any good hope of cure.

2. *Tumours of the oropharyngeal region.*—The term oropharyngeal is conveniently used to indicate a group of tumours which all begin within a comparatively small area and can all be exposed for removal by a single standard operation. The region centres about the tonsil and includes the anterior faucial pillar and the pharyngeal part of the tongue—that is, the part behind the circumvallate papillæ. Some further reference to the various growths occurring here is desirable.

(*a*) True tonsillar tumours. Of these epithelioma is the most common, but I have also met with endothelioma and mixed-cell sarcoma. Lymphosarcoma I have never seen at a stage in which the tumour offered the least prospect of curability by operation. Epithelioma, the most important tumour, tends to spread into the tongue to some extent, but chiefly downwards along the groove between the tongue and lateral pharyngeal wall into the pyriform sinus. This marked tendency to longitudinal spread renders free longitudinal exposure an essential necessity in the operative technique.

(*b*) Faucial pillar growths. These are always epitheliomata and are not at all rare. They begin on the front of the anterior pillar and soon involve the tongue and tonsil, tending to spread in exactly the same way as true tonsillar growths.

(*c*) Lingual growths. Two forms of epithelioma beginning in the tongue are included in the group. First, the common type which begins just at the lingual attachment of the pillar in the neighbourhood of the remains of the foliate papilla. The importance of this interesting vestige was first shown by Butlin. He called attention to the frequency with which

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it becomes irritated by the last molar tooth and gives rise to
the erroneous diagnosis of epithelioma. It must be remem-
bered also—and this increases the difficulty of diagnosis—
that this very spot is, in fact, a common starting point for
epithelioma.

The second form of lingual carcinoma which comes into
this group is that most formidable variety which begins in
the part behind the circumvallate papillæ, generally near the
middle line. It owes its seriousness to the remarkable
tendency it has to grow into the substance of the tongue
without in the early stages ulceration or projection at the
surface. Thus it happens that the disease runs for a con-
siderable time a practically symptomless course. Some dis-
comfort in swallowing, some slight limitation in protrusion
of the tongue, and some slight induration of its substance in
the hindmost part are for long the only signs. The most
difficult and dangerous of all the operations on the tongue is
necessary for the removal of the tumour, and the results in
my experience are correspondingly bad. Possibly good
results might be got if the clinical picture of the disease
were more widely known and operation fairly early in the
case rendered possible. It must always, however, remain
one of the graver forms, since the absence or ambiguity of
the early symptoms is such as often not even to arouse the
patient's attention.

3. *Tumours of the epilaryngeal region.*—The remaining
types we have to deal with are all epitheliomata, and this
fact simplifies to some extent the full discussion of them
which is necessary.

The term "extrinsic cancer of the larynx" is one which
has long been current as a name for tumours involving the
pharynx in the neighbourhood of the larynx. It served a
useful purpose in marking a distinction from the true intra-
laryngeal tumours or "intrinsic cancers of the larynx," but
it helped to encourage the belief that "extrinsic" tumours,
being essentially laryngeal, could be dealt with only by
extirpating the larynx. Without prejudice to the question
of the necessity or otherwise for laryngectomy, it would be
more in accordance with fact to describe all such tumours as

essentially pharyngeal in origin, and to reserve the term
laryngeal cancer for the growths beginning in and about the
vocal cord—that is, the " intrinsic " cancers.

Of such pharyngeal tumours as arise in the neighbourhood
of the larynx, those which begin in or near the margin of
the upper opening form a group so distinct in their cha-
racters and so uniformly accessible by a single operation,
that I venture to distinguish them under a special name as
the epilaryngeal tumours of the pharynx. These growths
may originate upon the aryteno-epiglottic fold or upon the
epiglottis itself. The latter situation is, in my experience,
decidedly the commoner. Neither form has any great
tendency to invade the essential parts of the larynx.
Perhaps, however, it would be better to say that at the time
of operation it is usually found that a considerable margin
of healthy tissue is present between the growth and the
vocal cords ; sometimes, indeed, the whole circumference of
the upper opening is affected before the vocal cords are
reached. The relative freedom of the body of the larynx in
these cases is probably due less to any essential benignity of
the growth than to the earliness of the period at which it
produces symptoms. There is, perhaps, no single feature
which affects the treatment of malignant disease of the
mouth or pharynx more favourably than the growth
being in a situation which leads to early and severe
symptoms.

The symptoms of the epilaryngeal group are an alteration
in the quality of the voice, giving it a peculiar " throaty "
character, hoarseness, difficulty in swallowing, and difficulty
in breathing.

The general behaviour of these growths as regards treat-
ment is favourable. They can be dealt with at least
frequently without laryngectomy, and permanent cure can
undoubtedly be obtained in moderately early cases. As far
as my small experience goes I should regard this group as
the most hopeful of all malignant pharyngeal tumours, and
I have no doubt that the treatment of them can be firmly
established as a standard measure with results satisfactory
as to safety, as to the absence of serious mutilation, and as
to the attainment of cure.

4. *Growths of the pyriform sinus.*—In the immediate neighbourhood of the larynx there occurs, however, another growth which presents a remarkable contrast with the epilaryngeal group as to symptoms, mode of extension, and curability. This is the tumour starting in the pyriform sinus, a tumour the frequency and importance of which have, I think, been greatly under-estimated.

I must remind you that the pyriform sinus is the deep recess which lies under cover of the ala of the thyroid cartilage between this and the upper opening of the larynx. Its external wall is the ala, its inner wall from below up the cricoid cartilage, the lateral part of the cricothyroid membrane and the structures of the aryteno-epiglottic fold. It is lined by a lax mucous membrane forming a diverticulum of the pharynx large enough in the adult male to admit the last joint of the thumb. Its cavity is quite inaccessible to laryngoscopic examination, which reveals only its mouth and would leave quite unsuspected the considerable recess that lies in front of this. It is usually just accessible to digital exploration, and can also be examined with the bronchoscope.

Growths originating here frequently run an absolutely latent course until they are far advanced. Often the first serious symptom is the appearance of a mass of glands in the neck, which on account of the absence of pharyngeal troubles the patient may ignore until they are quite inoperable. In the frequent cases of obviously malignant glands in the neck without ostensible primary tumour the sinus pyriformis should always be most carefully examined.

These tumours spread in an extremely characteristic way. Starting in close contact with the thyroid cartilage they early involve the perichondrium of this and extend diffusely beneath it, leading to a subperichondral growth of epithelioma, which spreads insidiously until it may have affected widely the ala of the opposite side. Meanwhile the cartilage itself is attacked and comparatively soon perforated near the spot where the growth starts. A swelling then forms on the outer aspect of the ala, and tends also to be surrounded by a diffuse subperichondral thickening. Such a swelling is sometimes mistaken for a gland, but can

usually be distinguished from such if the surgeon is familiar
with these cases.   Internally the growth tends to invade the
lateral wall of the larynx, where it causes an œdema visible
in the laryngoscope and later on fixation of the cord.   It is
quite rare for the growth to break through into the larynx
and ulcerate there, but it tends to spread round the cricoid
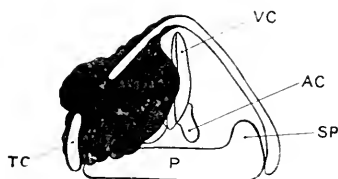in close relation to the perichondrium.   (Fig. 2.)

FIG. 2.

Diagram of section of larynx to show distribution of epithe-
lioma of sinus pyriformis. v c, Vocal cord. A c, Arytenoid
cartilage. s p, Sinus pyriformis. p, Pharynx. T c, Thyroid
cartilage.   The growth is in a moderately advanced
condition and at about the stage when surgical advice is
usually sought.   The diagram shows three characteristic
features of these growths: the penetration of the thyroid
ala, the slight involvement of the lumen of the pharynx,
the bulging inwards of the lateral laryngeal wall.   At such
a period no ulceration can usually be seen and the diagnosis
of gumma is frequently made.   Tumour shown in solid
black.

At this stage no symptoms beyond a slight hoarseness may
be present.   The only significant signs to be made out
usually are : (1) some œdema of the aryteno-epiglottic fold
and the lateral wall of the larynx below it ; (2) a persistent
pool of muco-pus between the arytenoid cartilage and the
lateral wall of the pharynx, while the opposite side is quite
free ; (3) some thickening on the outer aspect of the ala of
the thyroid and firmly fixed to it.   No ulceration is visible
by laryngoscopic examination.

Later the tumour emerges from the recesses of the sinus

and begins to attack the lumen of the pharynx. Here it tends to spread circularly and downwards towards the œsophagus. The extension round the pharynx, added to that round the larynx, gives the growth a figure-of-eight shape, and makes it the most formidable of all the pharyngeal epitheliomata.

The difficulty of diagnosis in anything like an early stage is scarcely credible. I have never seen a case in which at the time of operation the thyroid cartilage itself was not extensively invaded and perforated. In my experience, therefore, a total laryngectomy has always been obligatory. Fortunately, however, I believe this is the only tumour of the pharynx for which that terrible operation is invariably necessary, but it would seem that it must remain such unless our methods of diagnosis can be greatly improved, or until the desirability of exploratory operations on the pharynx in the presence of certain symptoms is generally accepted and enforced.

The chief cause of difficulty in the diagnosis is the laryngoscopic picture. This shows a smooth rounded swelling of the lateral wall of the larynx above the vocal cord, and usually no ulceration at all. These appearances lead to the diagnosis of an inflammatory lesion, usually gumma. The signs by which a correct opinion can be formed are the pool of muco-pus which fills the mouth of the sinus and betrays the presence of ulceration within, and the evidences of invasion of the ala of the thyroid. Sometimes a correct diagnosis can be made by external palpation of the larynx alone.

5. *Tumours of the hypopharyngeal region.*—A very well-marked group of tumours affects the lowermost parts of the pharynx below the opening of the larynx, and is thus conveniently described as hypopharyngeal. Certain tumours which occur somewhat beyond the limits of the hypopharynx of descriptive anatomy are so obviously similar that it is desirable to include them in the same group, which thus comes to comprise growths beginning in any part of the circumference of the pharynx below the upper opening of the larynx and on the posterior wall of the pharynx as high as

the level of the epiglottis. Such tumours. occurring as they do for the most part on the narrowest part of the pharynx, usually produce difficulties in swallowing comparatively soon. Diagnosis, therefore, is possible at a fairly early stage. The late period at which most of my cases have been submitted to operation has been due chiefly to the supposed inoperability of these tumours rather than to diagnostic difficulties. It is sometimes, however, difficult to distinguish clinically between a hypopharyngeal tumour and one of the pyriform sinus. This difficulty is serious when it occurs, for the type of operation undertaken in the two cases would be widely different. Some of these tumours have a tendency to invade the œsophagus diffusely, thus becoming wholly inoperable. When the œsophagoscope tube cannot be passed beyond the growth it may be impossible to detect this extension and an operation necessarily fruitless be undertaken.

Age and Sex Distribution of the Different Groups.

The facts as to the age and sex incidence of carcinoma of the mouth are well known, and I shall, therefore, not trouble you with the addition of my own small experience. I may, however, make the general statements that the disease is probably about ten times as common in men as in women, that in women it occurs at about the same age as it does in men, and that while women are subject to the forms which begin on the tongue and on the gum they seem to be very free from the form which begins on the floor of the mouth.

Growths of the pharynx present some remarkable peculiarities of age and sex incidence which need more detailed description. The *nasopharyngeal endothelioma* in the 10 cases I have had an opportunity of operating on has been a disease of the adult male, usually the young adult. I have seen a case in a young woman, but this is decidedly rare.

In the *oropharyngeal group* there were 9 cases of epithelioma of the tonsil or immediately adjacent parts. All the patients were males between 40 and 60. In addition, there was one mixed-cell sarcoma in an elderly woman and one endothelioma in a young man. In the *epilaryngeal* group

C

there were 10 cases, all epithelioma and all in males between 40 and 60.

The growths of the *sinus pyriformis* have rarely proved suitable for operation, so that the number in which the diagnosis was exactly determinable by inspection was extremely small. Nevertheless, the clinical picture is so characteristic that one's experience of inoperable cases may perhaps be taken into account. If this be done there can be no doubt that the disease chiefly attacks males between 40 and 60. I have met with one remarkable exception in the case of a typical epithelioma of the sinus pyriformis in a young woman aged 27. The diagnosis was confirmed in this case at operation.

Of the *hypopharyngeal group*, in 5 cases the diagnosis was confirmed at operation and all were in women, most of whom were between 40 and 50. Taking into account numerous other inoperable cases in which the diagnosis was practically certain, I should be inclined to say the lower age limit is too high, and that cases are met with as young as 30 or even under.

To sum up the age and sex incidence of pharyngeal malignant disease, one may say broadly that if a line be drawn across the pharynx from the posterior wall at the level of the tip of the epiglottis to the anterior wall at the interarytenoid notch, all epitheliomata above the line will be in middle-aged and elderly men, while all below the line will be in young and middle-aged women. (Fig. 1, A.)

PATHOLOGICAL TYPES AND AMENABILITY TO OPERATION.

I have already dealt with the peculiarities of the endotheliomata. My experience of sarcomata is not such as to justify any general conclusions ; we have, therefore, now to consider the epitheliomata only.

In the first place, I should like to state with emphasis my conviction that at the present time the only treatment of squamous epithelioma which gives any hope of cure is adequate removal by a carefully planned operation. If the sinister reputation of the disease is to be modified at all it

can only be through the study of its earlier clinical and pathological manifestations and by ceaseless attempts to improve the design and technique of operations.

Course of the Primary Growth.

It is a commonplace to all surgeons of experience, though apparently unknown to the general public, that cancer in its early stages and cancer in its later stages behave in relation to treatment as if they were two entirely different diseases. It is equally well known that in moderately advanced and even in " early " cases it is often impossible to say whether a given tumour is likely to be curable or not. Cases of an unpromising appearance sometimes surprise us by their satisfactory results, and more often, unfortunately, cases of the most hopeful aspect prove to be of the most inveterate malignancy. We are not, however, entirely without means of forming some estimate as to the curability or otherwise of a given case. A squamous epithelioma is typically a surface growth. If the evolution of the disease be studied throughout its course it will be found that the primary tumour remains for a considerable time essentially a superficial condition ; a large proportion of its bulk actually projects beyond the surface of the normal surrounding parts, while the deep aspect of the growth, although, of course, attached to the underlying tissues, can be felt to be marked off from them by an abrupt change of consistence— that is to say, in ordinary clinical terms the outline of the tumour is extremely well defined. After a variable period of growth a change in the physical signs of the tumour is established, and often somewhat abruptly. The deep extension of the growth seems to pass a critical point and then suddenly to increase. The projecting part of the mass no longer forms a large proportion of its bulk and the deep outline has become obscure. We no longer have to deal with the button-like mass inlaid, as it were, in the surface of the tongue, but with a tumour invading the sub-stance. This change in type of growth usually occurs within a few months of the beginning of the disease, but it is

sometimes delayed until a late period, and one then sees a large cauliflower growth, which in spite of its formidable appearance is by no means necessarily unsuitable for operation. Now, clinical experience shows that with this change in the mode of spread—often inconspicuous in the clinical features accompanying it—there is a very great increase in the difficulty of obtaining cure by operation. This observation is in accord with the admirable histological work of Cheatle upon the spread of cancer of the tongue. He has shown that when once the muscular substance begins to be freely invaded there is a very rapid and diffuse infection of the tongue muscles. It is in the quiet period before deep extension begins that epitheliomata can be removed with a practical certainty of cure. It is probable, however, that some few growths are of the diffuse type from the very early stages. Prognosis, therefore, should be based rather on physical signs than on duration.

Gland Involvement and its Varieties.

If local inveteracy were the principal difficulty in the cure of cancer, it is obvious that, once the distinction between the two grades of the disease was recognised, the results of cancer of the tongue at any rate would be much better than they actually are. As is well known, however, the difficulty lies in the involvement of the lymphatic glands, and there can be no doubt that at the persent time a large number of patients are cured of the primary focus of the disease only to die miserably from gland infection. We owe chiefly to Butlin the firmly based generalisation that as soon as the primary disease is established the liability to gland infection has begun, with the practical corollary that the gland operation should be as much a part of the treatment as the removal of the primary growth. So essential is this principle, and so invariable should be this rule, that I would go so far as to say that it has actually been a hindrance to progress that certain cases do not develop a gland infection although treatment has been limited to removal of the primary growth. All of us, no doubt, have had patients who

have refused to submit to the gland operation, and some few of whom have remained free from recurrence. The surgeon is, unfortunately, apt to be unduly impressed by such cases, and to be shaken in his belief in the invariable necessity of the gland dissection, which is at all times a difficult, tedious, and, from the patient's point of view, thankless procedure. It is now, however, quite definitely proved that any extensive experience will contain cases in which a gland dissection has revealed distinct foci of cancer, although the primary growth was small and superficial and no glandular enlargement could be recognised clinically. The only case in which I have felt justified in relaxing the rule as to the gland operation was in that of a patient aged 91. Here the treatment was definitely regarded as palliative only, and the fact that the patient survived the removal of the primary growth without the least trouble and lived for several years entirely free from recurrence is to be regarded as a fortunate accident.

The general rule for treatment should, therefore, be based on the knowledge that the primary growth and the possibility of gland infection appear practically together. A useful extension of the rule is the statement that the liability to gland infection bears no relation to the stage of the primary disease—that is to say, that for practical purposes there is no less liability to gland infection before the period of submucous invasion than there is after.

It is frequently assumed that when the glands are found clinically to be involved to any considerable extent the case is necessarily a hopeless one. My experience has not led me to share this view, and I think that a number of cases are lost through the undue pessimism of the surgeon discouraging him from submitting such patients to a thorough gland dissection. That there are, however, cases of even moderate gland invasion which defy all treatment there can be no doubt. Fortunately, we are not quite without clinical knowledge enabling us to some extent to discriminate between the two types. As long as the glands remain hard and well defined, even although they are quite numerous, the possibility of cure is still fair provided a really thorough dissection is done. If, however, the glands, though possibly

not numerous or very large, are ill defined, and give the impression rather of inflamed than carcinomatous glands, then the chances are strongly against any operation, however large, proving effective. A dozen stony-hard, sharply defined glands are less serious than a single one of which the outline is obscure and the substance rather yielding. In my material I find six cases of really extensive gland involvement which have been cured by operation. In two of these the enlarged glands were on both sides of the neck and extended down to the clavicle. Both patients have been free from recurrence for over four years.

When the gland enlargement has been moderate and of the favourable type I have never seen recurrence after a thorough systematic dissection.

Factors Influencing the Occurrence of Submucous Invasion.

The onset of diffuse extension to the underlying structures is, as we have seen, an event of crucial importance in the history of the primary growth. Capricious as it is, certain factors which influence its early or late occurrence can be made out.

(*a*) Duration of the growth. All epitheliomata ultimately tend to become diffuse, some slowly, some more rapidly. When diffuse extension is well marked and the growth has infiltrated and welded together any considerable body of structures outside the one in which it grew, the case is completely inoperable, and removal, although it seems to be anatomically satisfactory, will be followed immediately by recurrence. The recognition of this condition is largely a matter of experience, but in general one may say that a loss of definition in the palpable outline of a large tumour is the most important sign.

(*b*) Situation of the growth. The underlying structures may favour the extension of a tumour in various ways, so that the situation has a considerable influence upon submucous invasion. The situations in which early invasion is particularly prone to occur are the floor of the mouth on the

sublingual fold, the pharyngeal part of the tongue, and the sinus pyriformis. Consequently these three are the most formidable of all epitheliomata of the mouth and pharynx and can only be dealt with by the most extensive operations.

(c) Idiosyncrasy of the tumour. The nodular form of cancer of the tongue, one of the classical modes of onset of the disease, has a strong tendency to invade the muscular substance from the first, while it has little disposition to project from the surface or to ulcerate. It is of far more serious nature, other things being equal, than either the papillomatous or ulcerous form. Occasionally tumours of the epiglottis show the same peculiarity and penetrate the tongue early and deeply.

The combination of this variety of primary growth with the ill-defined inflammatory type of gland is unfortunately common and almost always defies the most resolute and extensive operation.

THE PLANNING OF THE OPERATION TO SECURE FREEDOM FROM RECURRENCE.

I. THE PRIMARY GROWTH.

Three types of growth present themselves for treatment, the superficial form (early cases), the form in which submucous invasion has begun or may be suspected (moderately advanced cases), and the form in which advanced submucous invasion has occurred.

(a) *Early Cases.*

Many of the growths on the tongue and in the epilaryngeal and hypopharyngeal regions are of this type. Experience shows that an excision of the tumour with a margin of tissue healthy to inspection and palpation not less than half an inch wide in every direction will give a practical certainty of freedom from recurrence. If the growth be certainly of

the superficial type there will be no need for the excision to
be especially free in any particular direction. Under special
circumstances the margin may even be less than half an
inch, but this should be regarded as undesirable. It is
extremely important that the growth should be centrally
placed in the part removed—any excess in one direction is
an unnecessary mutilation, while any diminution is a risk.
In order that such an excision may be carried out deliberately
and systematically it is absolutely essential that the surgeon
should obtain free and untroubled access to the part. The
provision of free access is, in fact, very often the most
important part of the operation.

(b) Moderately Advanced Cases.

Here a different standard must be adopted. The half-inch
margin is now an irreducible minimum to which it is very
undesirable to fall, and three-quarters to one inch should be
looked upon as the desirable limit. Moreover, there will
usually be certain directions in which the removal should be
especially radical. For example, in the nodular form of
cancer of the tongue or in cases originally superficial which
have developed submucous invasion, the muscles of the
tongue on the same side must be removed as far as their
attachments to the hyoid bone, as has been shown by the
histological work of Cheatle. In cases of growths on the
sublingual fold the removal posteriorly must be especially
free, as it is towards the pharynx that such tumours tend to
spread particularly. Growths of the tonsillar region must
be removed with a very free inferior margin for similar
reasons.

(c) Advanced Cases.

Most of them are obviously inoperable. The disease
seems to have reached an altogether uncontrollable
condition in which it invades the whole region in micro-
scopic outposts. In these circumstances an operation
may appear to be anatomically successful in removing
the growth with a good margin, but immediate recurrence is

the rule and the convalescence, which is distressing enough, merges into the re-established disease. The performance of such operations is a mere virtuosity of surgical technique which exalts the manifestation of skill above its purpose. Nevertheless. there are a few of these desperate cases in which the surgeon of experience will feel compelled to recommend interference.

One can never be absolutely certain that uncontrollably diffuse invasion has occurred, and the submitting of a patient to an unsuccessful operation, distressing as it is, is not so terrible a mistake as allowing to die of cancer unrelieved a patient who might have been cured. In my opinion these very large operations are never justifiable as palliative procedures, and should never be advised unless a distinct hope of permanent cure can be entertained. The actual danger of the operation is, with modern technique, not usually great enough to be an important factor in the decision

The Anatomical and Pathological Factors in the Planning of Operations.

It will be noticed that I have spoken of operations so far strictly in terms of removal of the growth and without any reference to the removal of organs or structures containing the growth. This seems to me an essential principle of the treatment of malignant disease. Most of the operations of surgery were originally designed as anatomical procedures. This was inevitable in view of the difficulties under which the surgeon of those days worked. In the absence of anæsthesia and knowledge of the causes of wound infection it was triumph enough if the surgeon succeeded in removing the tongue, the jaw, the larynx, or so forth. and the possibilities of success were so narrow that any modification of the anatomical procedure to suit the particular disease or an actual example of it was scarcely to be considered. At such a stage of development operative surgery could be perfectly well mastered in the deadhouse. The surgeon there learnt to remove various parts of the body with adequate dexterity, and actual practice was largely a

repetition of these chiefly anatomical exercises. The surgeon might amputate a limb, remove the tongue, or excise a joint most acceptably, guided entirely by his experience of operations on the corpse. Frequently, no doubt, the disease was satisfactorily dealt with, but it would be too much to expect that pathological processes should limit themselves to parts of the body which were easy to remove, and in consequence there was always a tendency on the one hand to sacrifice unnecessarily structures which, though not diseased, came within the limits of the operation, and, on the other hand, to spare diseased structures because they lay outside the anatomical region the operation was designed to remove.

To-day the whole basis of operative surgery has changed and the nature of an operation is determined by pathological considerations, anatomical requirements having been reduced by the increase in the resources of the surgeon to a secondary though still important place. There are, however, some vestiges of the influence of the anatomical period still remaining, and it is most important that these should be recognised. We are still apt to go on "excising the upper jaw for malignant disease," undeterred by the fact that in quite a number of cases after the operation has been carried out, in the venerable phrase, "secundum artem," the bulk of the disease, or possibly all of it, has been left behind. The same criticism applies to some extent to excision of the tongue and to laryngectomy for cancer. The gradual replacement of anatomical by pathological indications is going on rapidly, but there is perhaps less conscious recognition of the fundamental change of principle than there might be.

There are very few cases of an anatomical and pathological distribution of disease so exactly corresponding that a precisely designed anatomical operation removes the morbid condition and nothing else. Appendicitis and cholecystitis are instances that readily occur to one, but apart from these and a few such fortunate coincidences surgeons are having more and more to follow pathological requirements in their operations, and to overstep the anatomical boundaries which an older surgery was forced to remain within.

Nowhere is the tendency more marked than in the surgery of the mouth and pharynx, where the pathological requirements of the case must be supreme, so that the attainment of cure and the limiting of mutilation may be subserved at the same time. The formal purely anatomical operation retains, however, a function in providing means of access to the tumour. This function is so important that it should be recognised as a distinct part of the operation.

Since epitheliomata are essentially growths of the mucous membrane the provision of access renders necessary the free exposure of the mucous surface from which the tumour arises. Moreover, access must be allowed which provides for the free removal of the tumour, especially in the direction in which it particularly tends to spread.

We are now in a position to summarise shortly the essentials of an operation which shall give a maximal probability of cure : (1) Free exposure as a formal stage of the operation ; (2) exposure of the growth on its mucous aspect ; (3) exposure must be capable of indefinite extension along the line of spread of the tumour ; (4) removal of the tumour as a definite stage of the operation ; and (5) removal to be regulated entirely by the pathological necessities of the case, a precise margin of healthy tissue being included on every aspect, the extent of the margin and its increase in any special direction being determined by the nature of the growth. It will be seen that these requirements are left unsatisfied by many operations for cancer of the tongue carried out through the floor of the mouth, by operations for removal of tonsillar tumours through the same side of the neck, and by many laryngectomies.

II. THE GLAND OPERATION.

Two types of gland operation are necessary according to whether the glands are much involved or not.

(a) *Gland Involvement Clinically Slight or Absent.*

The dissection of the anterior triangle originally designed by Butlin and practised so successfully by him needs-

extension in two ways to render it an ideal procedure in preventing recurrence. First, a sufficient number of cases of very early bilateral gland involvement is met with to render the dissection of both sides necessary as an extreme precaution. In these early cases it can be carried out without extra risk.

Secondly, the operation should aim at removing the deep cervical chain of glands to its upper end against the skull, as it is in this region that recurrence is especially likely to occur. This involves a considerable increase in the horizontal extent of the dissection, which must be carried backwards under the sternomastoid to the posterior margin of the muscle. Completed in this way, the dissection will be found to comprise about four-fifths of the circumference of the neck, from which all lymphoid tissue has been removed. In these early cases the horizontal extension of the operation is undoubtedly more important than the vertical, which need not go below the thyroid cartilage. (Fig. 3.)

This posterior extension I regard as absolutely essential, though it makes the operation much more difficult. The spinal accessory nerve must first be found and isolated and raised up with the sternomastoid. The dense pad of fibrous and fatty tissue between the sternomastoid superficially and the splenius and levator anguli deeply is cut through at the posterior edge of the sternomastoid until the muscles are exposed and then it is turned forwards. I have never seen recurrence after this operation when it has been done in suitable cases.

(b) *Gland Involvement Extensive.*

In this type of case the bilateral operation cannot usually be done with safety at one sitting. Sometimes, when there was no evidence at all of involvement of the opposite side, I have omitted the second dissection with success. The enlarged glands generally surround the spinal accessory nerve, so that there is no question of preserving it. The sternomastoid and the jugular vein are also usually either

Fig. 3.

To show extent of gland dissection in early cases. The shaded
area is that from which all connective tissue, fat, and glands
must be removed.

involved or in suspicious relation to the glands so that they should be removed.

The muscle is divided at the clavicle, and the jugular vein tied and divided just above. The muscle and vein are raised together with the contents of the triangles. It is usually convenient to tie and divide the external carotid at its origin. The submaxillary triangle should always be cleared. The jugular vein is divided just above the digastric and the sterno-mastoid at its insertion. The operation is much easier than the ordinary bilateral dissection in early cases and takes much less time. Moreover, the convalescence is shorter, as, on account of the absence of the sternomastoid, there is no cavity for serum to accumulate in. The operation looks and sounds much more serious than it is and is usually surprisingly successful in eradicating the disease, unless the glands are of the diffuse inflammatory type. In addition to it, the dissection of the supraclavicular triangle is sometimes desirable and is not serious.

Occasionally in the first six months or so following upon a thorough gland operation a peculiar chronic enlargement of the glands bordering upon the area which has been dissected is to be observed. These become moderately enlarged and firm and then remain stationary, showing no further progressive change and no fixation. They do not lose the ovoid form and do not attain a long diameter greater than about three-quarters of an inch. The appearance is one decidedly alarming to the inexperienced, and is almost inevitably mistaken for a manifestation of recurrence. In fact, it is scarcely possible for the surgeon not to advise a further operation. Such operations I have repeatedly carried out, but microscopical examination of the glands removed has invariably failed to show any evidence of malignant disease. These experiences lead one to suppose that this kind of enlargement is in some way hypertrophic, in compensation. as it were, for the large tract of lymphoid tissue which has been removed. Great caution is, of course, necessary in deciding that in a given case the surgeon has to deal merely with this harmless condition. The moderate size of the affected glands and the absence of progressive enlargement are the most important features to be noticed.

These remarks apply only to cases in which the primary growth was an epithelioma. In cases of endothelioma I have never seen gland enlargement which did not prove to be a recurrence.

The Limits of Operability in Gland Involvement.

In a general way one may say that more mistakes are made in the direction of pronouncing tumours inoperable than in attempting operations which cannot be completed. The reason for this is that in advanced gland cases the principal mass is usually under the upper end of the sternomastoid and fixed to it near its insertion. This gives the erroneous impression that the growth is fixed to the spine. Glands beneath the muscle are also likely to appear ill-defined and diffuse when they are in fact not so.

When glands not under the muscle are indefinite and accompanied by brawniness of the skin and œdema it is generally quite useless to operate.

It is very remarkable how the common and internal carotids and the vagus escape involvement in gland masses until very late. Such masses tend to spread backwards and involve the muscles on the floor of the posterior triangle long before they attack the common carotid. When the common carotid and vagus are involved it is doubtful whether the operation should be carried out, and much would depend on the kind of primary growth and the condition of the patient. Removal of these two structures is a serious addition to the danger of the operation in itself, but it implies such extensive disease that cure is practically impossible. The limits of operability, then, lie less in technical difficulties than in the uselessness of the operation.

LECTURE II.

MR. PRESIDENT AND GENTLEMEN,—So far we have dealt entirely with problems connected with the cure of the disease, and have laid down the conditions which must be satisfied if cure is to be attained with any certainty. We now have to ask whether the technique at our disposal allows us to meet these requirements with a reasonable degree of safety to the patient. This chapter of the subject is concerned almost entirely with the infective complications of the operation. The primary operative risks, such as shock, hæmorrhage, and mechanical respiratory troubles, are so uncommon or so completely met by ordinary surgical measures that we need not consider them here.

THE DANGERS OF THE OPERATION.

The infective complications dangerous to life can be divided into two main classes : pulmonary infections and wound infections. Both of these are common and constant dangers in connexion with operations on the mouth ; they are much more serious in operations on the pharynx.

I. LUNG COMPLICATIONS.

That these still constitute a serious danger cannot be doubted, though it is perhaps sometimes thought that they are greatly less frequent than formerly.

Septic pneumonia is the essential condition met with. It is particularly likely to lead to suppuration, with the formation of single or multiple abscess cavities with gangrenous walls. The pus from these has the same smell as an

ulcerating epithelioma and all abscesses derived from the mouth and pharynx. The pneumonia is particularly fatal, and though I believe I have seen a few cases which have recovered, as a general rule the diagnosis brings with it the certainty of a fatal termination. Possibly operation on some of these cases of localised gangrene may be able to save a few. Two cases of post-operative gangrene of the lung in which I laid open the gangrenous focus were somewhat encouraging. In one, not, however, a mouth or throat case, the patient recovered; in the other the lung cleared up rapidly, but the patient died from a pyæmic focus elsewhere.

The causation of these pneumonias is a somewhat complex interaction of various factors, but a study of the evidence over a large number of cases and the effect of various prophylactic measures show that there are three processes at work. 1. The infection is derived from general sepsis of the mouth and from the septic ulceration of the growth. The extent of the ulceration is greatly influenced by the sepsis in the mouth, whether the growth is in the mouth or pharynx. 2. The lungs are irritated by the anæsthetic vapour and by blood. Probably the actual irritating material is mucus in which the anæsthetic is dissolved. The importance of the entry of blood alone has probably been greatly exaggerated. 3. The infective material is conveyed to the lungs by aspiration during the operation. Aspiration is favoured by any kind of respiratory obstruction.

There is one other mechanism I have omitted in this enumeration because it can be so easily and should be so rigidly excluded. This is the indiscriminate mopping out of the mouth and pharynx on account of the supposed necessities of the anæsthetist. It should on no account be allowed except under the most careful precautions, for by its means gross quantities of septic material are apt to be conveyed from the ulcer to the upper opening of the larynx, whence they are promptly aspirated into the lungs. In the few moments that elapse before the windpipe is opened it is scarcely ever necessary to sponge out the throat at all.

The importance of the different factors enumerated can be inferred from various clinical observations. In edentulous patients with but slightly ulcerated tumours pneumonia is

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scarcely to be feared. Accidental leakage past the pharynx or larynx plug during the operation is extremely dangerous. The influence of the anæsthetic is probably the least important factor. It is perhaps to it that the increase in the incidence of pneumonia with the length of operations is due. This increase is, however, seen only if the other factors are acting also. Short anæsthetics, even though all the other conditions are unfavourable, are very rarely followed by pneumonia.

The relative unimportance of entry of blood is shown by the occurrence of pneumonia after gland operations which are done before the primary growth is removed. These long and difficult operations are usually accompanied by great difficulty in maintaining a free airway and consequent excessive aspiration at the laryngeal opening. This is a strong argument against the gland operation being done first in cases with much ulceration.

The one precaution against pneumonia which I have found to be efficient is opening the larynx or treachea and plugging the airway higher up. I use it invariably for all cases except the smallest growths on the anterior part of the tongue. I find I have done a preliminary laryngotomy or tracheotomy more than 50 times. I have never seen any harm whatever come from it, and, on the contrary, a deal of good. Its advantages are numerous in addition to minimising the incidence of pneumonia : (a) The patient can be kept absolutely tranquil, breathing without effort and without coughing, so that the shock of the operation is greatly diminished by the absence of these dangerous and exhausting exercises. (b) It solves all difficulties of the anæsthetic. For these patients chloroform given through a laryngotomy tube is as nearly a perfect anæsthetic as we possess. (c) It greatly diminishes the risk of pneumonia. I have come to regard the gland operation done as a first stage as much more dangerous than the primary growth operation. In certain bad cases where the gland operation had to be done first I have done a preliminary laryngotomy and been much encouraged by the result. (d) It allows the complex operations of modern technique to be done deliberately and with the attention to detail they demand.

The procedure has no disadvantages. Laryngotomy, which should be reserved chiefly for mouth operations, can be done through a mere puncture which leaves an invisible scar, and takes three or four minutes. Tracheotomy should be used whenever the tube may have to be left in for some time. It takes a few minutes longer but is always quite easy. An interesting phenomenon is often observed in these cases, and that is the occurrence of periodic respiration after the tube has been put in and the preliminary apnœa has passed off. It is common in elderly patients and has no serious significance.

One important caution may be added, and that is that if there is the least reason to suspect any trouble whatever in breathing during the immediate post-operative period the tube should be left in. It can do no harm and may save the patient's life, as the shock of an attack of even partial asphyxia is very apt to be fatal in an enfeebled patient.

II. WOUND INFECTION.

This is little likely to be dangerous in the mouth, but immediately the anterior faucial pillars are passed the danger becomes a very serious one.

Acute septicæmia is not uncommon with large wounds of the pharynx. It generally begins at once and destroys the patient within a few days of the operation. Cellulitis is most serious with wounds low down in the pharynx. Wound infection from the mouth has certain marked and constant characteristics and tends to run a very definite course. All wounds which are allowed to come into contact with pharyngeal or oral mucus undergo necrosis of the surface with the formation of a definite slough. If the surface is quite open the infection does not tend to spread. The temperature is raised slightly and remains up for about a week, when separation of the sloughs with free suppuration begins. Usually for the first few days there is little or no pus formed. By the eighth day the temperature is usually quite normal, and by the tenth all sloughs have separated, leaving a clean granulating surface which is quite tolerant

of the pharyngeal contents. It is this specific and constant course which accounts for the limitation of secondary hæmorrhage to the eighth, ninth, and tenth days. It is extremely rare for it to occur outside these limits. If there is any interference with the drainage from the wound, especially if there is a pocket into which the pharyngeal mucus drains, a progressive cellulitis may be set up with extension to the mediastinum and a necessarily fatal termination. It has long been known that attempts to close large pharyngeal wounds may be very dangerous, and that leaving such cavities widely open and plugging them decidedly diminishes the risks. It does not, however, abolish them, and they remain a serious danger.

Secondary hæmorrhage is nowadays of very little import. ance in wounds in the mouth, and when it occurs is easily dealt with. It is much more likely to occur in connexion with pharyngeal wounds. I have lost three cases from it, and as two of them would almost certainly have been cured of their disease but for this disastrous complication I have a great respect for it.

All these wound complications are likely to be under-estimated if one's experience is limited to occasional operations. It is only when one has dealt with a series of cases that one finds that in the long run these conditions are very serious and threatening realities, and introduce into this whole branch of surgery an uncertainty which, combined with the uncertainty as to cure, is very discouraging both to surgeon and patient

It is clear that some fundamental modification of method is necessary if surgery in this region is ever to attain to the certainty which it has in certain other regions of the body. There are three methods which suggest themselves as afford-ing some hope of general applicability : (1) Preliminary immunisation of the patient against the organisms of the mouth and pharynx ; (2) preliminary disinfection of the mouth and pharynx ; (3) complete protection of the wound against contact with infective material during and after the operation.

1. *Immunisation.*

Of this I regret to say 1 have a very small experience, but such as I have is entirely without encouragement. Indeed, it seems to me highly improbable that the method will ever prove of much value in this branch of surgery. Possibly some protection against the septicæmias might be obtained, but I doubt if the local wound infections are likely to be made much less serious.

2. *Preliminary Disinfection.*

The mouth is the only source from which serious sepsis of wounds either there or in the pharynx can come. The desirability of preliminary cleansing of the mouth has long been recognised, and I do not suppose there is a surgeon who would operate on the mouth without some such pre- paration. Perhaps the need for such measures before operations on the pharynx is less generally recognised, but it obviously has only to be mentioned to be acknowledged. We may take it then that the scaling of teeth, the removal of stumps, and the use of disinfectant mouth washes are universal to-day. Whether these measures are regarded as ensuring any great improvement in the dangers of the more extensive operations is more difficult to say. I must confess that I have often found it difficult to satisfy myself that the most industrious use of these devices has yielded any appreciable diminution in sepsis. Speaking of the pharynx operations chiefly, I would say that as long as the patient has teeth there can be no approach to certainty that an operation will not be followed by dangerous sepsis. As soon, however, as we have to deal with edentulous patients a change in the grade of infection is at once obvious. Local infection of the wound surface still occurs, but spreading infections practically are not seen, sloughing is much less marked, and serious toxic symptoms are entirely absent. As representative cases I can recall an excision of a large

ulcerating sarcoma of the tonsil, a very extensive laryng-ectomy, and an excision of a large cancer encircling the hypopharynx. In each case the patient was edentulous, and in each healing was extraordinarily rapid. In fact, I can state positively that in the case of an edentulous patient I have never had the least cause for anxiety as to local sepsis after an operation on the pharynx. One of the reasons why cases in hospital practice usually do worse than private patients is that they do not acquire the clean edentulous mouth until later in life.

The advantages of a toothless mouth over the most elaborate efforts towards disinfection are so great that it is doubtful whether we should not always insist upon it as a preliminary to pharynx operations. I must confess that I do not always have the fortitude to do so. When a patient has just been told he has a very serious operation before him which will probably have to be done in two stages, it demands a great deal of determination on the surgeon's part to insist on the clearance of the mouth and another anæs-thetic. Nevertheless, it will usually be found that when the situation is explained most patients over 50 are glad enough to see the last of their teeth, which have generally by then ceased to be worth the trouble they increasingly give. From the point of view of the surgeon who has to deal with tumours of the pharynx modern conservative odontology is a very unwelcome triumph of science, and he cannot but be glad that there is a tendency amongst dentists to-day to admit that as soon as the teeth begin to give trouble in the elderly making a clean sweep of them is by no means the serious crime it was formerly thought to be.

If it is decided to remove all the teeth, and I repeat that this should always be considered most earnestly before all the graver operations, two practical points should be borne in mind. First, that in order to get the full advantage of the clean mouth the tooth sockets must be allowed com-pletely to heal before the main operation is done. This generally means a delay of a fortnight. If a preliminary gland operation is contemplated it may be done in the interval. Secondly, the removal of the teeth should be done with great care to inflict a minimum of injury. The dis-

plays of prestidigitation necessary when gas is the anæsthetic used, very frequently, if the number of teeth to be removed is large, leave the gums and jaws unnecessarily lacerated and liable to sepsis, and the patient suffering from an appreciable degree of shock. I think in these cases it is much better to give chloroform, and then very quietly and deliberately to remove the teeth, taking care that each one is extracted with a minimum of damage even to the gum.

3. *Complete Protection of the Wound against Contact with Infective Material.*

From the time when Whitehead introduced what was called his varnish many attempts have been made to protect wounds made in the mouth, at any rate from immediate contact with infective material. In my experience painting and plugging and such devices have been of no value. Again, for a long time the smaller wounds in the mouth have been stitched up with of course very satisfactory results. To a certain extent also larger wounds have been closed, but possibly not very systematically, for although many operators recommend the procedure they do not do so very warmly. One of the reasons is perhaps that very free access is necessary if a wound is to be thoroughly closed, and operators probably would scarcely look with favour upon increasing the extent of the operation solely for the purpose of suturing the wound. Again, the larger wounds, unless they are stitched up with certain precautions, are quite apt to behave unsatisfactorily.

Practically all wounds of the tongue can be closed and primary union obtained if there is free access and broad surfaces are brought together. Merely uniting edges of mucous membrane is quite useless, as they always slough. Deep mattress sutures of catgut should be used and the object of the surgeon should be to bring every surface of the wound in contact with another so that no cavity remains. In this way all oozing is stopped and in the great bulk of cases primary union is obtained throughout. Sometimes the edge of mucous membrane sloughs, but the amount of necrosis

is always inconsiderable. By this means the operation is practically deprived of danger, the convalescence is greatly shortened and made incomparably less distressing. Even fairly large growths of the tongue may be dealt with, the gland dissection done at a separate sitting, and the patient be ready to leave the hospital completely healed in a fortnight.

The advantages of this method are so obvious that the extension of it to the pharynx could scarcely fail to suggest itself. For some years I have been interested in attempting to develop a technique which should allow of this. The problem in the pharynx is much more difficult for many reasons. Nevertheless, I think it can be solved, and though I have no convincing body of cases successful as to cure to bring before you, I believe I can show that the technical difficulties of wound closure in the pharynx can be overcome. In operations on the pharynx it must be remembered that there are two wounds which need to be closed in order to prevent access of infective material to raw surfaces—viz., the wound made by removing the tumour and the wound made in opening the pharynx to obtain access to the tumour.

In operations on the oropharynx (e.g., tonsillar tumours) these two wounds are practically continuous and are sutured together. The only method giving satisfactory access to such growths is in my opinion one in which division of the jaw in front of the masseter is an essential part. Closure of the whole pharynx wound by numerous deep mattress sutures can usually be effected. It is, however, difficult to obtain complete union, and there is usually some leakage after a few days. This is quite small in amount, and at such a period of no serious importance. Occasionally in this region actual primary union can be obtained in the whole wound, but this is not possible except in the edentulous, and even then is scarcely to be expected. Still, such a success, even if a rarity, is very encouraging.

In the case of epilaryngeal tumours the wound of access and the wound of excision are distinct. On account of the presence of the tongue immediately in front of the latter enough tissue can be obtained

to secure closure provided very deep strong sutures are used.

The lateral incision in the pharynx (wound of access) can be readily closed provided no attempt at edge-to-edge suture is made but flat raw surfaces are brought together. I have several times succeeded in preventing any leakage whatever from the pharynx into the neck wound in these cases—a result particularly to be desired as one generally does these operations in one sitting, and therefore the neck wound is very large from the gland dissection and traversed by the carotid vessels. In a recent case, for example, I did a neck dissection of an extensive kind and then proceeded to remove a large cancer of the epiglottis. There was no leakage from the pharynx and the neck wound healed by first intention except for two small cavities which were deliberately kept open. In such cases, of course, the dangers of wound infection and secondary hæmorrhage are practically abolished.

When we come to the hypopharynx a fresh difficulty presents itself and has to be met in an entirely special way. It is that there is no spare tissue to allow the wound of excision being stitched up. Even after quite small excisions the wound cannot be got together except under great tension, which inevitably leads to additional sloughing beyond that caused by the sepsis. Moreover, in this region, even if the patient survives the risks incident upon infection, which she may well do, a serious stricture is sure to develop. It is clear, therefore, that some additional material must be provided, and fortunately a thoroughly satisfactory one is available in the skin. The method consists simply in turning a suitable flap of skin into the gap in the pharynx. A fistula is left at the pedicle of the flap and closed later. It gives rise to no difficulty, causes no interference with swallowing, and can be left indefinitely if desired. I shall enter into no technical details here, but must mention three points which are to be regarded as matters of principle. First, the flap must be cut in accordance with the situation of the tumour. If the latter is posterior in the pharynx the flap must come from the front of the trachea and have its pedicle over the sterno-mastoid. Secondly,

edge-to-edge suture is here also quite useless, and can only lead to sloughing. Surfaces of flap and surfaces of pharyngeal wall must be brought together by mattress sutures, the union resembling that used in suturing ends of bowel together. Thirdly, every effort must be made to preserve the surface over which the flap will lie from being infected during the operation. If these precautions be observed primary union of the flap into the pharynx can be obtained.

To summarise the considerations brought forward in the last section we may say that the essentials of an operation which shall be satisfactory from the point of view of safety are : (1) the prevention of aspiration of infective material into the lungs (laryngotomy or tracheotomy) ; (2) the adequate preparation of the mouth (removal of teeth) ; and (3) protection of the wound from infection (wound closure).

Technique of Operations.

In this section I propose to give some account of the actual methods of operating I have come to regard as the most suitable for the various tumours. It will not be possible to deal with them in any great detail, and I shall limit myself to essentials.

Results.

As a preface, however, I feel I should lay before you some account of the results of my own operative experience. These are neither extensive nor successful, and they therefore possess very little interest for anyone but myself, to whom they display an instructive series of mistakes, and failures to appreciate the significance of the various problems. Coming as they do from a period when an attempt was being made to evolve more certain methods of dealing with these forms of disease the cases are almost all of them types of advanced cancer. The few early cases contained in the series were there as it were incidentally, for they presented no particularly urgent problems for solution, whereas

difficult and even desperate cases were as far as possible
selected. For this reason the results as regards cure cannot
be regarded as anything but unsatisfactory. Again, many, if
not most, of the earlier operations were done by methods
which I should not hesitate to condemn to-day, but which
formed perhaps necessary steps in the evolution of less
defective procedures.

I find I have operated on 32 cases of malignant disease of
the mouth exclusive of the lips. Of these, 4 died from the
operation. In 5 the patients were lost sight of, leaving 27
in which the termination is known. Of these, 7 were
apparently cured. In 2 of these 7 cases, however, the
period of immunity has lasted only 18 months. They are
included as both were very early. All varieties of epithelioma
are included, and most were very late cases. The figures as
to immediate mortality are respectable ($12\frac{1}{2}$ per cent.); the
figures as to cure (25 per cent.) are to my mind far from
satisfactory. Later methods would, it is to be hoped, give
something much better.

Oropharyngeal Group.

The cases operated on were 14. Of these, 11 were tonsillar
or immediately about the tonsil ; 3 were of the pre-epiglottic
part of the tongue.

Of the tonsillar cases 2 died from the operation, 3
developed recurrence of the disease, in 3 the result is not
available (1 too soon after operation, 2 cannot be traced),
and 3 were cured.

The 3 cases cured were an extensive ulcerating sarcoma,
an early epithelioma, and a very advanced epithelioma with
gland involvement. All these have been free from recurrence
for over three years.

Of the pre-epiglottic lingual cases 2 died from the opera-
tion and 1 developed recurrence. These figures illustrate
very well the seriousness of this type.

The figures for the tonsillar group tend to exaggerate the
seriousness of the disease. Certainly much more than 25 per
cent. should be curable.

Epilaryngeal Group.

The cases operated on were 10, all distinctly advanced cases, some markedly so. Of the 10 cases, 2 died from the operation, 3 developed recurrence, 1 has been operated on recently, and 4 were cured.

Of the 4 cases cured, in 2 the growth was of the epiglottis and in 2 of the aryteno-epiglottic fold. In 1 a laryngectomy was done, but in the other 3 local excision of the growth only. All have been free from recurrence at least two and a half years. The 3 who were treated by local excision of the growth recovered practically a normal voice and perfectly normal deglutition. In all of them there was extensive gland involvement. These figures may be regarded as fairly satisfactory. All the 4 cured were desperate cases on account of the primary growths and the glands both being of serious dimensions. That no mutilating operation was necessary in 3 cases is encouraging. The percentage of cure should, however, be at least 50.

Hypopharyngeal Group.

The cases operated on were 5, and no cure is to be recorded ; 2 died, 1 from mediastinitis and 1 from secondary hæmorrhage. Of the 3 remaining cases, in 1 the operation was not completed, in 1 the patient died from intercurrent disease within six months, and in 1 the patient lived in normal health for a year and then developed an aberrant recurrence high up behind the pharynx. Two of the cases illustrated very successfully the advantages of wound closure by a transplanted skin flap.

SEQUENCE OF GLAND OPERATION AND OPERATION ON PRIMARY GROWTH.

An important question to be decided in every case is whether the disease is to be attacked in a two-stage or a

one-stage operation, and as a corollary whether the gland operation or that on the primary growth should be done first.

In the great majority of cases there can be no doubt that the two-stage operation is necessary. The attempt to accomplish in one sitting the two very complex procedures can only lead to excessive danger to the patient or a risk of incomplete removal of the disease. The only exception to this rule that I at all commonly allow myself is in the case of epilaryngeal tumours. Here the primary growth cannot be attacked until the glands have been removed, and on account of the situation of the growth the gland operation even cannot be done with any safety without a preliminary tracheotomy.

As to the sequence of the two stages the following general rules are those upon which I decide.

1. If the primary growth is in such a situation and of such size that rapid union can be obtained after removal of it, then the first stage should be on the primary growth and the second on the glands. This is chiefly in early tongue cases. In such cases the whole treatment can usually be completed in a fortnight.

2. Where the primary growth is such that rapid union is not probable (e.g., where the jaw has to be divided), the gland operation should be done first. This has its special disadvantage in the danger of pneumonia of an extensive neck operation when there is an ulcerating growth in the mouth, but the special advantage is that the gland operation is much easier when done first.

3. Where the glands hinder access to the primary growth three courses are possible—(*a*) Gland operation first (glands very large). Tracheotomy is usually necessary. (*b*) Primary growth and *partial* gland operation first (usually tonsillar cases). (*c*) Single-stage operation (epilaryngeal cases).

4. Where the primary growth or gland mass is of uncertain operability the one which is the more doubtful should be attacked first.

THE ESSENTIAL STEPS OF THE OPERATION ON THE PRIMARY GROWTH.

1. Every operation for removal of a tumour must begin with a definite stage devoted to obtaining access to the mucous surface of the tumour. This is usually a perfectly formal anatomical procedure which applies to all cases when the same region is affected.

2. As soon as the tumour is fully exposed a systematic attempt must be made to disinfect the region, and during the subsequent removal of the growth every effort must be made to preserve the wound from contamination. The surface of the ulcer should be cauterised, the surrounding mucous membrane cleansed with spirit, and the region of the tumour packed off so that mucus is prevented from flowing into the wound.

3. The tumour is then excised with the size and form of surrounding margin dictated by the nature of the case.

4. The wound from which the tumour has been taken must be closed by suture and such other plastic procedures as are necessary should be carried out.

TECHNICAL DESCRIPTION OF OPERATIONS.

Nasopharyngeal Group.

Exposure of the tumour.—The only method of obtaining free access to the nasopharynx is by osteoplastic resection of the upper jaw. The classical form of this operation on the lines of the ordinary excision of the jaw gives very poor exposure, and I have found it a great advantage to mobilise the malar bone with the maxilla. This makes the operation actually easier and gives quite a fair view of the naso-pharynx. In order to avoid the very ugly œdema of the lower eyelid which so often occurs, I carry the incision upwards through the eyelid just outside the punctum lacrymale, along the orbital margin inside the lid, and then from the outer canthus downwards and outwards over the cheek. (Fig. 4.)

FIG. 4
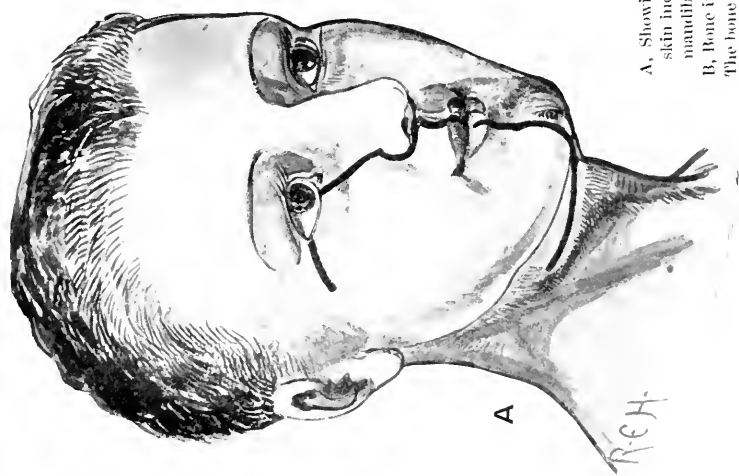
A, Showing skin incision for osteoplastic resection of maxilla and malar bone. The skin incision used in obtaining access to the tongue or tonsil by the lateral transmandibular route is also shown.

B, Bone incisions for osteoplastic resection of maxilla and malar bone. The bone incision for the lateral transmandibular operation is also shown.

Removal of tumour.—No special feature of this needs discussion. Hæmorrhage is not difficult to control, and plugging need not be firm or bulky.

Closure and reconstitution.—The jaw can be fixed in position by a stout wire just below the nose. The wire generally has to be removed later. After a few months' time very little deformity is visible, and the mobility of the eyelid has generally been completely restored.

Oral Group.

In dealing with this group no detailed description is necessary, and I shall refer merely to a few points of technique which have struck me as particularly important or as often overlooked.

Choice of operation.—In my experience all growths of the " superficial " type can be dealt with by an intrabuccal operation with or without splitting the cheek. When the tumour is of the nodular type or has passed into the stage of submucous invasion, and when the tumour involves or begins in the floor of the mouth, I believe it cannot be removed adequately without division of the jaw. All the submandibular methods have the disadvantage that the growth cannot be freely inspected or disinfected before the removal of it has been begun, and that subsequent closure of the wound is difficult or impossible. 1 have never used the lateral submandibular method at one time associated with the name of Kocher, and I do not expect ever to do so. It is, in fact, no longer recommended by its author, and would not have been referred to in these lectures, which deliberately ignore the historical side of the subject, had it not been so conspicuously the beginning of the modern treatment of cancer of the tongue, and therefore by no means the least of the debts we owe to the great and ingenious surgeon whose name it bore.

The intrabuccal operation.—The only point of importance in this operation is the adequate fixation of the tongue

before the excision is begun. The ordinary method of passing a thread through the front of the tongue is very apt to lead astray because the muscular substance, being extensible, stretches after the anterior part of the incision has been made, and this leads to the free margin behind the growth being defective. A thread should be passed deeply well behind the growth and the tongue held out with this ; another should be passed on the mesial side and another in front. When these threads are held taut the area from which the growth is to be excised is kept relaxed, so that a constant margin can be maintained all round during the excision. Moreover, the posterior thread keeps the tongue against the angle of the mouth and prevents the entry of blood.

Splitting the cheek is a most useful measure, and should be used much more than it is. It is sometimes condemned on account of the conspicuous scar it is supposed to leave. Such an objection is not valid, because if the wound is sutured with mattress stitches so as to make the line of suture project no depression of the scar follows. I have used this incision several times in women, and have obtained a scar that was practically invisible.

The transmandibular operation.—This should never be done by continuing downwards the posterior end of the cheek-splitting incision as originally designed by Langenbeck. Such an incision permanently paralyses the lower lip. The jaw is best exposed by a flap, the incision running down through the lower lip in or near the middle line and continuing backwards beneath the jaw to the anterior edge of the sternomastoid. (Fig. 4, A.) Care is taken to incise the mucoperiosteum well in front of the place where the bone is to be sawn, so that the incision in bone and soft parts do not coincide, and the risk of infection of the former is diminished. I have used many methods of fixing the divided jaw. The least unsatisfactory is a wire near the lower border. The great defect of the operation is infection of the bone. Unfortunately, it is common and usually troublesome. In the most favourable cases the wire has to be removed sooner or later. The liability to this complication must be regarded as the chief defect in the technique of access to the mouth
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and tonsil, but the advantages of the operation with regard to adequate removal of the growth are so great that I do not think it can be dispensed with. It must never be forgotten that the object of the surgeon is to cure the disease, and that the one indispensable quality of an operation is its suitability for this purpose.

The operation is admirably adapted for giving access to large growths of the tongue, to growths of the floor of the mouth, pharyngeal part of the tongue, and tonsillar region. It allows of almost indefinite extension of the wound downwards.

Oropharyngeal Group.

Small growths of the tonsil not extending beyond its surface may be removed through the mouth after the cheek has been split. It is not desirable to enucleate the tonsil in these cases, but the growth should be freely cut out with a good margin of the surrounding tissues. Such wounds can be closed completely, In these early cases it is never necessary to remove much of the soft palate, and this point should receive attention, otherwise a little careless freedom may permanently modify the voice. Large growths can only be reached by the transmandibular operation. (Fig. 4, A and B.) Excision of the tonsil through the neck on the same side should never be done, as no inspection of the growth can be made before the removal is begun.

Epilaryngeal Group: Transthyroid Pharyngotomy.

The upper opening of the larynx lies under cover of the ala of the thyroid and the great cornu of the hyoid. It can be exposed undisturbed only if these structures are removed. The operation of which this is an essential part may conveniently be called transthyroid pharyngotomy. (Fig 5.)

As I have already said, the operation has usually to be done in combination with the gland operation. Consequently the extensive neck wound is liable to infection from the pharynx. Should this happen the result can scarcely

FIG. 5.
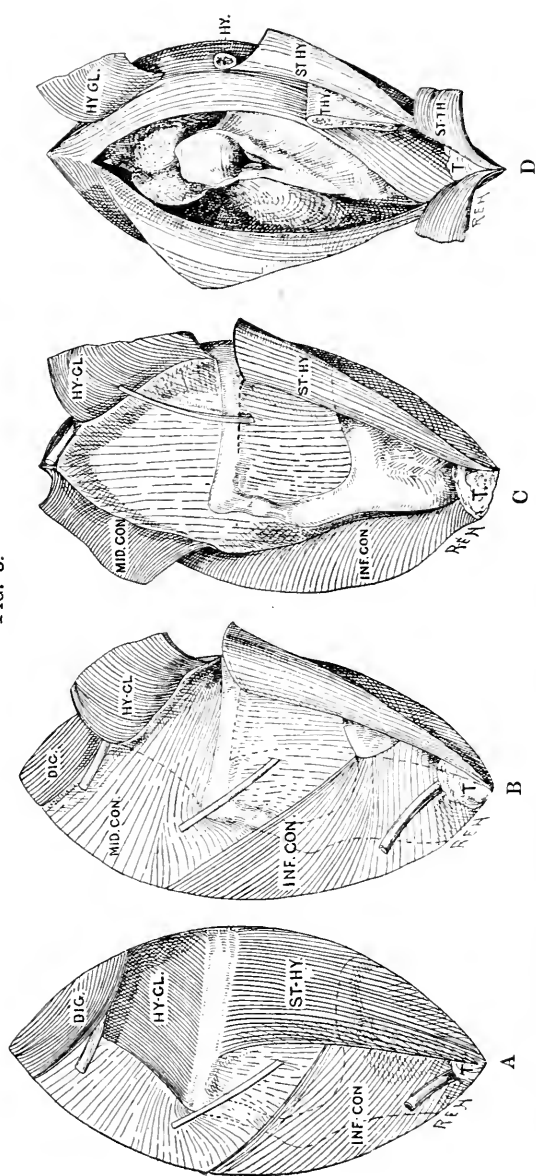
Four stages in the operation of transthyroid pharyngotomy. A, Lateral aspect of pharynx at end of preliminary gland dissection. B, Hyoid muscles reflected. C, Pharyngeal constrictors reflected, aponeurosis of pharynx exposed. D, Lateral wall of pharynx incised, epilaryngeal region exposed. ala of thyroid prepared for removal. D, Lateral wall of pharynx incised, epilaryngeal region exposed; great cornu of hyoid and

fail to be serious. The carotid vessels, carefully exposed by
a clean dissection of them, run through the midst of the
wound, and secondary hæmorrhage from them might quite
possibly occur. A series of elaborate precautions have to be
made to secure the neck wound from contact with infective
material.

The incisions for the gland operation include a longi-
tudinal one over the anterior part of the sternomastoid.
The deep fascia is divided, not in this line, but an inch or
more further forward. It is then turned back from over the
muscle in the form of a flap attached posteriorly. If the
glands are extensive the whole sternomastoid is removed,
otherwise only its anterior part. The gland dissection is
then completed, the external carotid being divided at its
origin. (Fig. 5, A.) Before approaching the pharynx the
fascial flap already described is stitched to the pre-vertebral
muscles behind the pharynx and internal to the carotid
vessels. In this way the whole of the posterior part of the
wound and the carotid vessels are securely shut off from the
part which will be exposed to infection from the pharynx.

The inferior constrictor is now detached from the thyroid
and cricoid cartilages and turned back. The stylopharyngeus
is detached from the posterior border of the thyroid, and the
great cornu of the hyoid is freed from its muscles (hyoglossusl
middle constrictor, &c.). (Fig. 5, C.) The pharyngeal wal,
is separated from the deep surface of the great cornu and
the ala, and these two are removed with the thyrohyoid
ligament connecting them—the great cornu at its joint and
the posterior two-thirds of the ala. It is important to excise
the whole great cornu and a full two-thirds of the ala,
otherwise the cut surfaces are apt to become infected and
give trouble from necrosis.

The wall of the pharynx—aponeurosis and mucous
membrane—is now freely exposed unopened. Through it
the tumour is to be felt and some idea of its size and situa-
tion obtained. The pharynx is now incised longitudinally,
its edges being secured with sutures by which they can be
held up so as to protect the surrounding wound which is care-
fully packed with gauze. (Fig. 5, D.) Plugs are pushed up
into the mouth and nasopharynx so as to prevent mucus

trickling down into the wound. The tumour having been investigated is freely excised under guidance of sight and touch. During excision of the epiglottis the strong attachment of the latter to the body of the hyoid should be remembered, otherwise it may be felt and mistaken for an extension of the tumour. It may be necessary to carry the incision right down to the vocal cords. This wound is closed by deep strong mattress sutures which must obliterate its cavity completely.

The pharynx wound is then closed with at least two rows of suture, bringing raw surfaces together. The constrictor may then be stitched back in place. The wound should be drained by two plugs in its anterior most superficial part, the plugs going down to the pharynx wall. A large tube should be left in the posterior isolated part of the gland wound for 24 hours.

The tracheotomy tube should always be left in and is usually needed for a week. Feedings should be by a soft rubber catheter passed into the œsophagus. Swallowing should not usually be tried for about ten days or a fortnight. Generally there should be a complete absence of leakage from the pharynx and the greater part of the gland wound should heal by first intention.

The Sinus Pyriformis Group.

For these laryngectomy must generally be done. I propose to say nothing about the technique of this. It is important to ascertain how much of the pharyngeal wall is involved in order to make adequate provision of flaps to make good the defect. Into the elaborate arrangement and designing of these it is not possible to enter here.

The Hypopharyngeal Group.

The transthyroid method of approach is always desirable, but the incision must be in the form of a flap to provide for reconstitution of the pharynx. The disposition of the flaps

in accordance with the situation of the growth is seen in the diagrams. (Figs. 6 and 7.) It is most important to make out beforehand the exact site of the tumour. Great care should be taken not to reflect the flap the least degree further than is necessary. If there is any doubt of the size

FIG. 6.
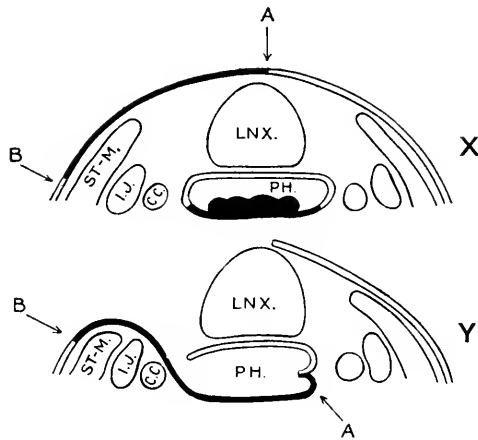
To show disposition of skin flap in operation for removal of hypopharyngeal growth — tumour on posterior wall. X, Before removal of tumour. Skin flap and parts to be removed shown in solid black. Y, After removal of tumour; skin flap in place. A marks situation of apex of flap. B marks situation of base of flap. LNX, Larynx. PH, Pharynx. c c, Common carotid. I J,' Internal jugular. ST-M, Sterno-mastoid.

of flap needed it should always be made too large rather than too small. The whole art of plastic surgery by skin flaps lies in a complete absence of tension.

Especial care should be taken to prevent mucus from getting on to the raw surface left by removing the tumour. The flap must be stitched to the cut edge of the pharynx by

numerous mattress sutures. In all operations of this and
the preceding types the suturing is extremely tedious, and
demands from the surgeon endless patience. There need be
no hurry whatever to close the fistula by dividing the pedicle
of the flap and stitching it over.

FIG. 7.
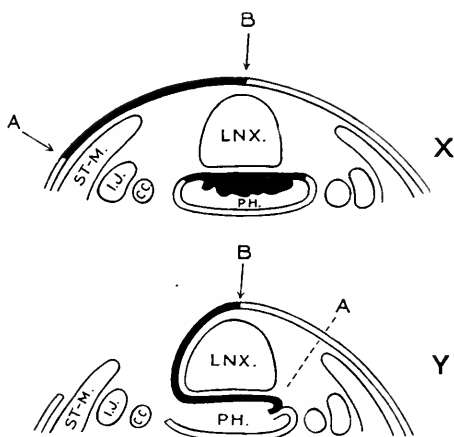
To show disposition of skin flap in operation for removal
of hypopharyngeal growth — tumour on anterior wall.
X, Before removal of tumour. Skin flap and parts to be
removed shown in solid black. Y, After removal of tumour;
skin flap in place. A marks situation of apex of flap.
B marks situation of base of flap. The fascial flap to protect
the carotid vessels is not represented.

In the early post-operative period the patient should be fed
by tube through the fistula. The skin of the flap is apt to
become bright red during the first week or so of its contact
with the pharyngeal contents. In the absence of œdema
and induration this must not be assumed to indicate suppura-
tion beneath the flap.

In concluding these lectures it is perhaps desirable for me to make the observation that they were written deliberately as an exposition of my own experience and of the conclusions I have been able to draw from it. Any dogmatic statements of fact or inference carry with them, therefore, the implicit qualification of their personal origin, and are in no way supposed to be of wider validity than exactly that which is warranted by the limited experience they embody. Furthermore, the various technical procedures recommended are given for the usefulness, such as it is, which they seem in practice to possess, and the statement of them, therefore, is not intended to include the implication that any of them is described here for the first time.

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XXIX.   ON THE LIPOLYTIC ACTION OF THE TISSUES.

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(Received April 7th, 1913.)

The following experiments were carried out to test the lipolytic activity of the various organs towards the neutral fats.

It is only comparatively recently that such enzymes have been demonstrated in the tissues; their presence was inferred previously from the action of tissue extracts on simple esters, such as monobutyrin, etc. That these are by no means the same, has been shown by Cohnstein [1904] for the castor-oil seed.   Arthus [1902] showed a similar difference for blood serum.

Nencki and Lüdy [1887] tested the lipolytic power of tissues on amyl salicylate and found that the tissue extracts worked best in an alkaline medium.

Hanriot [1896] used monobutyrin and demonstrated a lipolytic ferment in all tissue extracts except the thyroid. The enzyme ceased to act when a certain degree of acidity had developed and could continue when the acidity was neutralised. He also showed that the tissue extracts could hydrolyse the ethyl esters of formic, acetic, propionic and butyric acids.

Arthus [1902] drew attention to the errors in Hanriot's observations and was unable to confirm his work. Kastle and Loevenhart [1900] experimented with ethyl butyrate and found that the ferment was closely attached to the cells, and that liver extract was more active than the pancreatic on this ester, but that the pancreas could hydrolyse the esters of the higher fatty acids more readily than those of the lower.

Siebert [1900] studied the action of pancreatic extracts on egg yolk, and further, showed that the blood serum is incapable of splitting lecithin.   Subsequently Umber and Brugsch [1906] experimented with tissue extracts, using egg yolk as their emulsion of neutral fat. The various organs were washed free from blood, then finely ground up with kieselguhr and the juice

pressed out with a hydraulic press. Two series of experiments were per-
formed, one with the organs from an animal killed whilst digesting, the other
in starvation. One series of experiments was conducted under aseptic
conditions, the other under toluene.

These observers concluded that the tissue extracts can hydrolyse the fat
in egg yolk and that during digestion the pancreatic extract is the most
powerful, closely followed by that of the spleen, but that the liver and
intestinal mucosa are more powerful than the pancreas. Further that
activating bodies would appear to be present in some of the organs.

In the following series of experiments it was intended to study the
action of the various tissue extracts on:

       (1)   Egg yolk.
       (2)   Artificial emulsions of lecithin.
       (3)   Lecithin not in a state of emulsion.
       (4)   Chyle obtained from the human subject.

The tissues were ground up finely in a mortar, mixed with an equal bulk
of normal saline and pressed through a press so that the tissue extract con-
sisted of a fine suspension of the tissue in normal saline. The tissues were
removed under strict aseptic precautions; pigs' and dogs' organs were chiefly
used. In the case of the pigs' organs, these were removed in the slaughter-
house in gauze soaked in $2\cdot5\,^o/_o$ carbolic, the outside was removed with a sterile
knife and the tissue transferred to a sterile mortar and ground up with sterile
normal saline. The dogs' tissues were obtained from healthy dogs, which
were anaesthetised and bled to death. The animals were subsequently
washed out with sterile normal saline. No toluene experiments are recorded,
because it was found that even adding toluene up to $2\,^o/_o$ did not inhibit the
growth of organisms which were capable of splitting up egg yolk very readily.
The "fat" containing emulsions were also prepared under strictly aseptic
precautions and sterilised.

The mixtures of "fat" and tissue extract were incubated at 37° for
15–20 hours. At the end of that time they were examined directly and
culturally for possible bacterial contamination and any showing this were
rejected. The method of estimating the effect of the tissue extracts was to
determine the total amount of "fat" present by boiling the mixture of un-
incubated material with sodium carbonate for some time on the water bath,
and then, after acidulating with sulphuric acid, extracting with ether. The
ethereal extract, after removal of the mineral acid, was then treated with
$N/10$ KOH to neutralise the fatty acids, and then hydrolysed with alcoholic
potash, evaporated, and taken up in water, acidulated with sulphuric acid

and the liberated fatty acids extracted with ether, which was then freed from sulphuric acid by shaking up with water. The ethereal solution of the fatty acids was titrated against N/10 alcoholic potash and then reckoned in terms of oleic acid; 1 c.c. N/10 KOH = 0·0282 g. oleic acid. The incubated mixtures were neutralised with sodium carbonate, well heated on the water bath and acidulated with sulphuric acid to liberate the fatty acids which were extracted with ether and purified as before. The amount of fatty acid was thus determined by titration with N/10 alcoholic potash.

In some of the experiments it became necessary to separate oleic acid and other high fatty acids from any lower acids, such as lactic acid, which might be formed from the carbohydrates. This was done by having a double series of mixtures; in the one the total fatty acids were determined in the way mentioned above, in the second the mixture, after neutralisation and boiling, was treated with sulphuric acid to liberate the fatty acids and then treated with ammonium sulphate, according to the methods of Magnus Levy, to separate the lower from the higher fatty acids.

A. *Effect of tissue extracts of various organs on sterile egg yolk mixture, containing 0·5 % sodium carbonate.*

10 c.c. tissue extract was used with 20 c.c. of yolk suspension. Results expressed in c.c. decinormal alkali.

No. of Exp.	Pigs' organs			Total fats as fatty acids	Fatty acids liberated	% hydro-lysed
1	Pancreas	...	...	53·2	48·0	90·0
	Liver	...	...	55·8	20·5	36·7
	Spleen	...	...	53·8	20·2	37·5
	Pancreas + 5 c.c. Spleen		...	53·4	40·0	75·0
	,,　　,,　　,, (the spleen was first boiled)		...	53·4	40·0	75·0
	Liver + 5 c.c. Spleen ...		...	56·0	21·6	38·6
	Pancreas + 5 c.c. Spleen		...	54·2	38·6	70·1
	Serum	...	...	Not determined	0·0	0·0
2	Pancreas	...	...	53·6	30·6	57·0
	10 c.c. Bile ...	...	...	51·8	19·08	36·7
	Pancreas + 5 c.c. Bile ...		...	51·0	30·0	55·5
	Pancreas + 5 c.c. Bile + 5 c.c. Serum			54·6	30·8	56·0
	10 c.c. Serum	...	...	Not determined	0·0	0·0
3	Pancreas	...	...	54·0	37·2	68·2
	Liver	...	...	55·2	21·8	39·5
	Kidney	..	...	54·6	20·4	37·87
	Muscle	...	...	54·4	20·2	37·0
	Spleen	...	...	54·4	21·6	40·0
	Pancreas + 5 c.c. Spleen		...	54·8	39·1	71·0
	Muscle + 5 c.c. Spleen		...	54·4	21·0	39·87

Dogs' Tissues.

5 c.c. of extract + 20 c.c. of yolk suspension in each experiment. Results expressed as before.

					Total fats	Fatty acids	%hydrolysed
Dog 1	Spleen	...	...	...	56·1	20·5	36·5
Hungry	Liver	...	...	...	56·8	20·5	36·0
animal	Pancreas	...	...	...	55·9	22·8	40·9
	Kidney	...	...	...	56·3	20·2	35·8
	Liver + Spleen (5 c.c. of each) ...				57·1	22·0	38·0
	Pancreas + Spleen (5 c.c. of each)				56·2	37·0	65·8
	Pancreas + 5 c.c. of Serum			...	58·4	37·5	66·2

5 c.c. of extract + 20 c.c. of yolk suspension in each experiment. Results expressed as before.

					Total fats	Fatty acids	%hydrolysed
Dog 2	Pancreas	...	...	...	54·2	41·0	75·5
Digesting	Pancreas + Serum	...	...		54·4	37·0	68·0
animal	Serum	...	...	...	—	0·0	0·0
	Liver	...	...	...	55·0	20·8	37·8
	Spleen	...	...	...	54·3	20·2	37·0
	Pancreas + Spleen	...	...		54·6	44·5	81·5
	Pancreas + boiled Spleen	...			54·6	41·5	77·0

5 c.c. of extract + 20 c.c. of yolk suspension in each experiment. Results expressed as before.

					Total fats	Fatty acids	%hydrolysed
Dog 3	Pancreas	...	...	...	52·8	30·0	57·0
Hungry	Pancreas + Liver (5 c.c. of each)				53·6	34·0	63·4
animal	Pancreas + Spleen (5 c.c. of each)				53·2	33·8	61·2
	Spleen	...	...	...	53·9	21·2	40·0
	Liver	...	...	...	53·4	22·0	40·1

Human Tissues.

Removed twelve hours after death. 20 c.c. of egg yolk and 10 c.c. of the tissue suspension. Results expressed as before.

	Total fats as fatty acids	Fatty acids liberated	% liberated
Pancreas	56·2	46·0	81·8
Pancreas and Liver (5 c.c.) ...	57·0	48·0	84·3
Pancreas and boiled Liver (5 c.c.)	57·0	49·0	85·9
Liver	56·8	21·0	37·0
Spleen	56·0	21·4	38·2
Liver + 5 c.c. Spleen	57·0	23·0	40·3
Pancreas + 5 c.c. Spleen... ...	56·6	48·6	85·6

Sheep's Tissues. Quantities as before.

	Total fats as fatty acids	Fatty acids liberated	% liberated
Liver	51·8	20·2	36·6
Spleen	54·0	19·8	37·0
Liver + Spleen (5 c.c.)	55·0	20·4	37·0
Liver + boiled Spleen (5 c.c.) ...	55·2	20·4	37·0
Pancreas	53·8	30·2	56·4
Pancreas + 5 c.c. Spleen... ...	54·2	32·0	58·6

From these experiments it will be seen that the tissues have the power of breaking up the lecithin when it is exhibited to them in the form of egg yolk emulsion.

In all cases the pancreas has a much more powerful action than any other tissue extract, and there is from these experiments no distinct evidence of

any kinase capable of augmenting the activity of the ferments. The only example of this effect occurs in one of the experiments with the tissues of a dog in a fasting state, but in the other experiments with the organs of a dog, and with those of pigs and sheep, which are always slaughtered in a fasting condition, there is absolutely no evidence of any activating ferment in any of the tissues. In these respects these experiments do not agree with those of Umber and Brugsch [1906].

The above results, however, like those of Umber and Brugsch, take no notice of the formation of the lower fatty acids, which Magnus Levy [1902] showed were formed during the incubation of tissues from the carbohydrates present. In order, therefore, to eliminate this error, the following experiments were performed in double series; in one the total fatty acids were estimated, in the other the lower fatty acids were estimated after separation by ammonium sulphate, the difference between the two being due to the amount of fatty acid liberated by the hydrolysis of the fat.

In the following series of experiments 10 c.c. of tissue juice were incubated with 20 c.c. of yolk suspension in 0·5 % sodium carbonate at 37° for 18 hours. The results here are in terms of $N/10$ NaOH as before.

No. of Exp.	Pigs'	Total fatty acids found	Lower fatty acids	Higher fatty acids	Total fat in terms of fatty acids	% hydro- lysed
1	Liver	23·0 c.c.	7·6 c.c.	15·4 c.c.	52·0	29·6
	Spleen	21·0	3·2	17·8	51·2	34·7
	Kidney	18·0	4·0	14·0	51·3	27·3
	Pancreas	39·0	1·5	37·5	51·0	73·5
2	Sheep's					
	Pancreas	31·0 c.c.	2·0 c.c.	29·0 c.c.	51·0	56·8
	Liver	19·0	6·1	12·9	51·8	27·9
	Spleen	12·8	1·8	11·0	51·2	21·5
	Kidney	13·2	4·0	9·2	51·4	17·9
3	Dogs'					
	Pancreas	38·0 c.c.	1·4 c.c.	36·6 c.c.	49·2	74·4
	Liver	18·0	4·1	13·9	49·8	27·8
	Spleen	17·0	5·7	11·3	49·0	23·0
	Muscle	12·0	5·2	6·8	49·3	13·7

These experiments do not very greatly alter the results of the previous experiments, and confirm the lipolytic power of the various tissue extracts towards egg yolk emulsion.

B. *Experiments with liver extracts on lecithin, not in a state of emulsion.*

Weighed quantities of lecithin were placed in sterile flasks and sterilised. Then sterile tissue extract was added and allowed to act for varying intervals in the cold or warm.

In Exp.	1.	19 % was broken up.	} In 16 hours at 37°.
,,	2.	23 % ,, ,,	
,,	3.	18 % ,, ,,	In 14 days at 4°.
,,	4.	56 % ,, ,,	,, 28 ,, ,,

The result in each case should be somewhat higher, because no account was taken of the amount of lecithin in the liver extract added. It is interesting to note that jecorin could also be found in all these experiments after incubation.

C. *Action of tissue extracts on chyle.*

The chyle was obtained from a healthy young man suffering from lymphatic obstruction, producing lymphangiectasis in one lower limb. The chyle could be obtained under aseptic conditions in large quantities after a period of blocking the fistulae in the lower limb. It contained from 1·3 to 1·6 g. of fat per cent., and from 0·064 to 0·08 g. of lecithin.

The lipolytic ferment in the chyle was destroyed by heating to 60° for an hour, thus also sterilising the fluid.

Sodium carbonate was added to make a 0·5 % solution.

In these experiments a double series was made in order to determine the relative amounts of higher and lower fatty acids.

20 c.c. of extract of the finely pounded tissue were added to 50 c.c. of chyle and incubated for 18 hours at 37°. Results expressed in c.c. of N/10 NaOH.

No. of Exp.	Pigs'	Total fats	Fatty acids found	Lower fatty acids	Higher fatty acids	% hydro-lysed
1	Pancreas	24·0	18·8	1·6	17·2	71·5
	Liver	27·2	13·0	6·4	6·6	24·2
	Spleen	23·1	5·6	2·6	3·0	13·0
	Kidney	24·8	9·4	4·2	5·2	21·0
2	Pigs'					
	Pancreas	22·9	14·2	0·8	13·4	58·5
	Liver	25·8	9·2	3·8	5·4	20·9
	Spleen	23·2	7·4	4·8	2·6	11·2
	Kidney	24·4	6·8	3·0	3·8	15·6
3	Sheep's					
	Pancreas	22·0	13·2	1·0	12·2	55·4
	Liver	27·1	9·2	4·0	5·2	18·0
	Spleen	22·4	5·6	3·2	2·4	10·7
	Kidney	25·0	6·0	2·0	4·0	16·0
4	Dogs'					
	Pancreas(10c.c.)	21·6	15·0	1·0	14·0	65·0
	Liver	30·3	13·4	4·2	9·2	30·3
	Spleen	24·7	6·5	2·8	3·7	15·0
	Kidney	26·6	8·2	3·1	5·1	20·0

These results show that a certain amount of the fatty acids found in the

incubated mixture is due to the formation of lower fatty acids. Further, that the tissues have the power of liberating higher fatty acids when incubated with chyle, but as chyle and the tissues contain not only neutral fat, but lecithin as well, the question then arises as to the relative proportion hydrolysed by the tissue ferments. Finally the figures are quite small when compared with those obtained by using egg yolk.

To determine this question a series of experiments was carried out in which the lecithin, the total amount of fats and the higher fatty acids formed were determined before and after incubation.

For this purpose three sets of each mixture were made. The lecithin was determined by extracting the material with alcohol and ether, evaporating, taking up in ether, precipitating by acetone and determining the phosphorus in the precipitate by Neumann's method.

1 c.c. N/2 NaOH = 0·014331 g. of lecithin.

Lecithin contains 66 % fatty acids.

Quantities as before. Results reckoned as fatty acids in terms of N/10 alkali.

Exp. 1. Pigs'	Liver	Pancreas	Spleen
Total fats	25·1 c.c.	21·1 c.c.	23·5 c.c.
Lecithin	0·261 g.	0·0902 g.	0·1504 g.
Lecithin fatty acids ...	6·1 c.c.	2·1 c.c.	3·5 c.c.
Fatty acids liberated ...	10·1	14·0	6·8
Lower fatty acids liberated	4·2	1·8	3·0
Higher ,, ,,	5·9	12·2	3·8
Lecithin left	nil	nil	nil
Fatty acid in Lecithin ...	6·1	2·1	3·5
Fatty acid found ...	5·9	12·2	3·8

Exp. 2. Dog's Liver. Quantities as before.

Total fats	25·9 c.c.
Lecithin	0·339 g.
Lecithin fatty acids	7·9 c.c.
Fatty acids liberated	12·2
Lower fatty acids liberated	4·0
Higher ,, ,, ...	8·2
Lecithin left	nil

Fatty acids in the lecithin = 7·9 c.c. N/10 NaOH.

,,   ,,   found liberated = 8·2   ,,   ,,

Exp. 3. Quantities as before.

Sheep's	Liver	Spleen	Kidney
Total fats as fatty acids ...	30·4 c.c.	28·9 c.c.	30·2 c.c.
Lecithin	0·244 g.	0·177 g.	0·235 g.
Fatty acids in Lecithins ...	5·7 c.c.	4·2 c.c.	5·5 c.c.
Fatty acids liberated ...	11·3	8·4	7·8
Higher fatty acids liberated	5·5	3·9	5·3
Lower ,, ,,	5·8	4·5	2·5
Lecithin left ,,	nil	nil	nil

Exp. 4.

Pigs'			Liver	Kidney	Spleen	Spleen + Liver (10 c.c. of each)
Total fats	...	...	26·8 c.c.	25·1 c.c.	21·2 c.c.	21·1 c.c.
Lecithin	...	...	0·2178 g.	0·1576 g.	0·108,) g.	0·3152 g.
Fatty acid in lecithin	...		5·1 c.c.	3·7 c.c.	2·6 c.c.	7·4 c.c.
Fatty acids liberated	...		8·3	5·2	6·5	13·7
Lower fatty acids liberated			2·8	2·1	4·0	6·1
Higher	,,	,,	5·5	3·1	2·5	7·6
Lecithin	...	...	nil	trace	nil	nil

In all these experiments it will be noticed, with the exception of that with pancreatic extract, that the amount of fatty acids liberated corresponds to the amount of fatty acids present in the lecithin, and that in all cases the lecithin is practically completely hydrolysed.

Evidence of the inability of the lipase of the liver to attack neutral fat is obtained from experiments on aseptic autolysis at 4°. Fat expressed as c.c. $N/10$ NaOH %.

Duration of autolysis (days)	Dogs' Tissues	Sheep's Tissues
0	16·2	21·0
7	16·6	20·4
21	15·8	21·6
42	16·2	22·4
91	16·8	—
168	—	22·8
224	—	22·4

This shows that ordinary fat is not hydrolysed, but that lecithin is hydrolysed at 4°. These results indicate that the liver, spleen and kidney contain a lipolytic ferment which attacks lecithin quite readily, but has no apparent action on the simple glycerides of the higher fatty acids even when presented in the form of the finest emulsion as in chyle, or as they exist in the tissue itself as is seen in the autolytic experiments.

It is possible that the reason of this lies in the fact that lecithin can form in water a colloid suspension, and so can be more readily attacked, but the previous results show that lecithin can be readily split up even when presented to the tissue extracts in a very coarse form. The other and more probable explanation would appear to be that when the glycerides of the higher fatty acids are taken to the liver or other tissues they are converted into lecithins and stored up free or in combination with the protein as the invisible unstainable fat in the normal organ and in this form are easily hydrolysed by the lipolytic ferment as required. This view seems the more probable from the results of Leathes and Kennaway [1909], who showed that the liver desaturates fats brought from the food or fat depots; this agrees with the high iodine values of the lecithins, showing that the lecithins are

formed from these desaturated fatty acids. Further, it is important to note in the quantitative estimations of the "fats" in the liver, etc., that by far the greatest amount is accounted for by the lecithins, nearly 90 %.

D. *Experiments to ascertain the effect of reaction on the lipolytic power of the organs.*

In each of these a double series of experiments was performed to ascertain the amount of higher fatty acids.

Pig's Liver. 10 c.c. of extract with 20 c.c. of egg yolk suspension.

1. *Effect of Alkali.*

With g. Na₂CO₃	(%)	Total fatty acids	Lower	Higher	Total fat	% hydrolysed
0·05	(0·16)	14·4	6·0	8·4	40·8	20·7
0·1	(0·32)	21·6	7·6	14·0	40·8	34·3
0·15	(0·5)	23·2	7·4	15·8	40·8	38·7
0·2	(0·66)	18·2	6·1	12·1	40·8	29·6
0·3	(1·0)	10·1	4·0	6·1	,,	14·9
0·4	(1·33)	6·0	2·1	3·9	,.	9·0

Same quantities as above, but 30 c.c. water added.

0·05	(0·08)	12·5	4·6	7·9	40·2	19·6
0·1	(0·16)	20·0	6·0	14·0	.,	34·8
0·15	(0·24)	21·4	6·6	14·8	,,	36·8
0·2	(0·33)	16·2	4·6	11·8	,,	29·3
0·3	(0·5)	9·3	2·4	5·9	,,	14·6
0·4	(0·66)	5·0	2·0	5·0	,.	7·4

Thus it will be seen that the activity does not depend on the percentage of alkali present, but on the total amount.

2. *Effect of lactic acid.* The quantities used were as before. Incubation 16 hours. The amount of lactic acid is in c.c. of the decinormal solution.

Dog's Liver. 10 c.c. of extract with 20 c.c. of egg yolk solution and all made up to 40 c.c.

C.c. N/10 acid	Total fats c.c. N/10 alk	Total fatty acids found	Lower	Higher	% hydrolysed
2	48·2	20·2	6·8	13·4	27·8
4	,,	23·8	7·9	15·9	32·9
6	,,	24·9	9·3	15·6	32·6
8	,,	23·1	12·4	10·7	22·2
10	,,	20·8	13·0	7·8	16·2

Pig's Liver. Quantities as above.

2	48·2	18·6	8·1	10·5	21·8
4	.,	23·8	9·7	14·1	29·2
6	,,	24·2	10·4	9·8	20·3
8	,,	21·2	11·8	9·4	19·5
10	,,	19·8	14·1	5·7	11·8

SUMMARY.

From these experiments we can conclude that :

(1)   The tissues possess a true lipolytic ferment.

(2)   The lipolytic ferment, with the exception of the pancreatic lipolytic ferment, can only hydrolyse phosphatides and jecorins, but not ordinary fats.

(3)   The ferment is capable of acting in an alkaline or acid medium.

(4)   There is no evidence of a kinase in the spleen.

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THE EXCITING CAUSES OF VENTRICULAR FIBRILLATION IN ANIMALS UNDER CHLOROFORM ANÆSTHESIA.

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Contents.

INTRODUCTION.

Retrospect.

A SERIES of cases of sudden death in animals under the influence of chloroform was alluded to in a preliminary communication[14] to the Physiological Society about two years ago, and it was therein shown that these deaths were due to fibrillation of the ventricles. In a later communication[15] I described in detail the manner of death occurring during the stage of the induction of chloroform anæsthesia, and it was shown that in these cases likewise the ventricles fibrillated.

I have now succeeded in producing this cardiac phenomenon by a number of experimental methods.

The key to the solution of the problem was afforded by observations upon *cardiac irregularities* which developed spontaneously in cats when the strength of the chloroform was diminished, or on cessation of administration, these irregularities frequently assuming a form which was identical with that which was likewise observed to be an invariable antecedent to the act of fibrillation. Further light was afforded by the observation that small quantities of adrenalin injected into the blood of the lightly chloroformed animal caused ventricular fibrillation, an action likewise described in the afore-mentioned preliminary communication.

These observations were confirmed and their relationship expounded in an investigation undertaken in conjunction with Dr. T. Lewis[21] into the electro-cardiographic phenomena of chloroformed cats. The irregularities were therein recognised as the result of premature contractions (or extrasystoles) arising from various foci in the ventricles and exhibiting grades of complexity ranging from single extrasystoles arising in a single abnormal point up to a rapid succession of extrasystoles from several different foci (multiple tachycardia). When the ventricles exhibit these latter complicated irregularities, they are in a state of potential fibrillation, fibrillation being but a progressive stage in the chain of events.

It is evident in studying ventricular fibrillation that great importance must be attached to the observation of these irregularities as constituting antecedent stages, and as affording minor evidences of a process which, in a more intense form, would terminate in complete cardiac syncope. The conclusions of other investigators regarding the source of origin of these irregularities have therefore suggested the lines of investigation that I have adopted in tracing out the exciting causes of ventricular fibrillation.

There are two main theories extant relating to the production of ventricular abnormalities in hearts held to be acting under normal conditions : (1) that supported by Hering,[9] Knoll,[13] and Heidenhain,[8] which refers their production to an increase in the intracardiac tension, further supported by MacWilliam's view[22] that ventricular fibrillation is purely mechanical in origin ; (2) that supported by Rothberger and Winterberg[25] and by Garrey,[6] which refers their production to nervous influences.

The theoretical considerations thus briefly indicated are in many respects complicated and obscure, but it is evident that either or both of these two views may be held to afford an interpretation of the adrenalin reactions. Adrenalin, as is well known, is held to act upon the myoneural junctions of the entire sympathetic distribution, thus stimulating the heart in addition to producing a general vasoconstriction, and hence this research in taking the adrenalin reaction as a starting point, has branched off into two well-defined paths. From this paper, however, with the exception of one important reference, I am excluding the whole of the details of my work relating to the pressor influences under chloroform, for although at the beginning I favoured a theory of reaction to a raised intracardiac tension and found much apparent confirmation of it, it became evident that many of the pressor influences were associated with cardiac augmentor influences, and ultimately I failed to find definite evidence that pressor changes bore any relation of importance to the production of these described cardiac irregularities under chloroform. That portion of the work will be therefore more conveniently considered later in a separate paper.

On the other hand by pursuing the alternative theory of a direct cardiac action, I have been led to constant and coherent results which are open to a definite theoretical interpretation, although this interpretation is not that of the production of the irregularities through influences which are *necessarily* of a nervous character, as will appear in the course of this paper. The conclusions at which I have thus arrived have such an important practical reference that I have felt constrained to embody in this paper the essential features of my research whilst certain theoretical points remain under consideration, leaving the detailed account of many of my earlier experiments to be considered in a following paper.

I have pleasure in here expressing my indebtedness to Dr. T. R. Elliott and Dr. T. Lewis for the assistance I have received from them in following up my subject ; the special knowledge which each possesses has been very helpful in many respects.

Methods of experiment.

All the experiments herein described were performed upon cats. The blood-pressure curves were registered from an artery, generally the carotid, by means of a Ludwig's mercury manometer or a Hürtle's membrane manometer, employed independently, or, as in some cases, conjointly according to a method described by Sollman and Pilcher,[28] of damping the mercurial oscillations down to their smallest dimensions by means of a screw clamp on the rubber connecting tube, so that a quantitative indication only of the mean blood-pressure is inscribed without affecting the more delicate record of the individual heart beats traced simultaneously by the lever of the membrane manometer. A typical example of such a combined curve is shown in Fig. 6.

The mercury manometer, when used alone, affords a very graphic representation of fluctuations of blood-pressure and cardiac pauses and is therefore the most ready means of recognising the onset of irregularities, but it is liable to slur over, or totally obscure the individual abnormal beats, and it is for the proper analysis of these that the Hürtle manometer is found useful. This latter instrument has however the disadvantage of occasionally rendering the more extreme degrees of irregularities (multiple tachycardias) as an apparently regular, or almost regular sequence. The two forms of record thus reciprocate, and their respective features are illustrated in the curves reproduced in Fig. 1, *a, b* and *c*.

A half saturated solution of sodium sulphate was employed to fill the manometer and its connecting tubes.

The chloroform vapour was administered by passing it, mixed with air in suitable proportions, through the small end of a funnel which covered the head of the animal (the so-called *ad plenum* method of administration). The percentage of vapour was regulated by means of an appliance elsewhere described[17]; this was attached to the inlet pipe of a Brodie's pump, a distended rubber bag on the delivery tube of the latter serving to convert the intermittent into a continuous stream.* The animals were anæsthetised by submitting them from the start to the influence of a 2% vapour, which was continued without intermission; the percentage being ultimately increased sufficiently to produce complete muscular relaxation.

In order to perform control experiments upon a cat not affected by any anæsthetic, and also in order to study the induction of chloroform anæsthesia from the first moment of the administration, two methods were adopted. (1) That described by Brooks[2] whereby an artery was prepared under a general anæsthetic one day, and on the next a cannula was slipped into it without difficulty under a local anæsthetic only. In some cases I employed the special form of metal cannula described by Brooks. (2) The cat was rendered anæsthetic by passing a stylet into the foramen magnum and cutting across the crura cerebri. Sometimes it was possible to avoid injury to the bulb and then natural respiration was maintained, otherwise artificial respiration was carried out in these cases. In both of these two methods chloroform narcosis could be subsequently induced in the usual manner.

The successful demonstration of the results hereinafter described depends essentially upon a precise control of the anæsthetic—this degree of anæsthesia must, on the one hand, suffice to obviate the supervention of spontaneous irregularities, and on the other hand be insufficient to depress the heart to the point of modifying or preventing the onset of these irregularities when an attempt is made to excite them, or to depress the reflex mechanisms involved in some of the experiments. For these reasons prolonged dissections or severe operations are inadvisable, and negative

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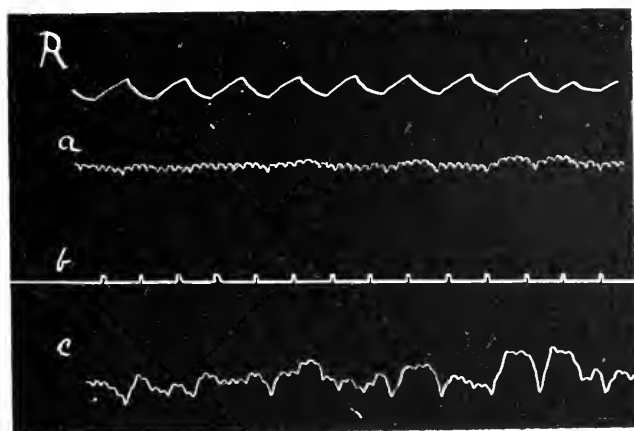*For purposes of artificial respiration the bag was discarded, and the intermittent stream employed.
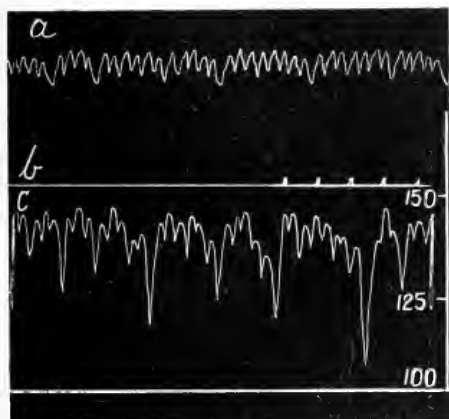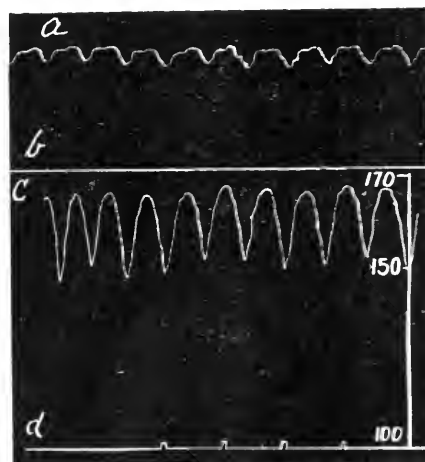
Fig. 1A.

Fig. 1B.

Fig. 1C.

Fig. 1. Types of irregularities occurring under light chloroform anæsthesia.

A.   Hürtle and Ludwig curves recorded simultaneously from separate carotid arteries. R. Respiratory curve. a. Hürtle curve. b. Hürtle abscissa and time signal marking seconds. c. Ludwig curve. The Ludwig abscissa is not shown. These curves illustrate a rapid type of irregular tachycardia under chloroform. The Hürtle manometer accentuates the individual pulse beats, often, as in this case, with little appearance of irregularity. The mercury manometer accentuates the irregular nature of the curve, but obliterates the individual beats. The fluctuations in pressure bear no relation to the respiratory rhythm. Rate of beat—270 to 300 per minute.

B.   Contrasted Hürtle and Ludwig curves, recording consecutive periods of an irregular tachycardia with beat rate of 180 per minute. a. Hürtle curve. b. Hürtle abscissa and time signal marking seconds. c. Ludwig curve. d. 100 mm. mercury pressure level.

C.   Contrasted Hürtle and Ludwig curves, recorded during consecutive periods of a simple form of irregularity, i.e., bigeminal beats. a. Hürtle curve. b. Hürtle abscissa. c. Ludwig curve. d. 100 mm. mercury pressure level, and time signal in seconds.

The Ludwig curves appear to represent a regular and slow beat of 90 per second. The Hürtle curve demonstrates the beats as bigeminal and the rate doubled (180 per second).

results especially are valueless under such conditions, frequently the best results are only obtained in animals in which the necessary dissections had been previously carried out and much of my work was performed upon such surviving animals.

Artificial respiration was employed for exceptional experiments only, and such exceptions are stated in the text. Ventricular irregularities are less readily exhibited in animals under its influence.

Definitions.

(1) The terms *light* and *deep anæsthesia* require definition. They can be expressed largely in terms of the percentage administered, but not precisely, for the degree of anæsthesia is likewise affected by the *duration* of the administration—thus an animal may be only lightly anæsthetised by a short duration of a high percentage, a fact which has in the past led to confused inferences ; the converse is also naturally the case. With these reservations a vapour of 1% or thereabouts may be taken to imply light anæsthesia, but the lighter the anæsthesia the more favourable are the conditions for the production of ventricular fibrillation, and this applies not only to the experiments with adrenalin but in the case of most of the remaining methods employed to bring it about. It is important to note that the fact of the animals being lightly anæsthetised does not imply an anæsthesia insufficient for ordinary light operations, in fact it has frequently been my practice to work with animals entirely unrestrained either in head or limb, the only fixed connection being the arterial cannula clamp. Powerful sensory stimulations such as the excitation of a sensory nerve with a strong faradic current under such circumstances naturally sometimes produce reflex movement, but all ordinary manipulations were performed without difficulty and without interference with the recording apparatus although the anæsthesia came within my category of light anæsthesia.

(2) The symbol " V.F." is employed to represent the words " ventricular fibrillation " in the tabulated accounts of experiments.

(3) The term " multiple tachycardia " is employed to denote a rapid sequence of ventricular extrasystoles arising from multiple foci.

Types of irregularities.

Several well defined types of irregularities occurring under chloroform have been previously fully described and illustrated.[21] In addition to these it is common to observe disorderly successions of normal and irregular beats presenting various complicated records which cannot be analysed by manometric methods alone. Such types of irregularities are exemplified in Fig. 1, and many of the succeeding figures.

Recovery from ventricular fibrillation.

Ventricular fibrillation is recognised as the most deadly form of cardiac syncope, in fact it was at one time a moot physiological point whether the heart ever recovered from it. As the result of an extensive experience of this

condition I am able to state that spontaneous recovery in the cat is not infrequent ; it may occur after a few seconds of fibrillation (Fig. 2 and 10) or indeed after a period of one or more minutes (Fig. 11). As a general rule, however, the heart neither recovers spontaneously nor can it be restored to its normal functions by any method in general use for the treatment of cardiac syncope, and it eventually dies from asphyxia of its tissues. It does appear, however, that the proportion of recoveries may be increased by certain special measures, direct rhythmic compression of the ventricles being particularly effective, but the discussion of these matters I reserve for a later communication.

I. The direct cardiac effect of adrenalin.

(a) *Aspects of the reaction of general application.*

The adrenalin reaction has been so fully dealt with elsewhere[14] [18] [& 21] that a very brief re-statement will suffice for the purposes of this paper. In animals anæsthetised with chloroform to a full surgical degree the reaction consists of the usual rise of blood-pressure with or without the accompaniment of a ventricular tachycardia, never followed by ventricular fibrillation. Under light chloroform anæsthesia the tachycardia is invariable, and in the great majority of instances permanent ventricular fibrillation ensues.

These observations have now been very fully established by a large number of experiments with this drug ; they are of fundamental importance in relation to the study of ventricular fibrillation under chloroform. The reaction is modified by various conditions which it is unnecessary to deal with fully in the present paper, but given a healthy animal with a well-sustained circulation and inhaling chloroform at a low percentage, the respiration being natural and unembarrassed, then the intravenous injection of 0·065 m.g. of adrenalin chloride, or frequently of a less amount, entails the almost certain onset of ventricular fibrillation.

Ventricular fibrillation produced in this, or indeed in any other way under chloroform, is generally permanent, and the heart dies from cessation of the circulation. Occasionally the heart recovers spontaneously, it may be in a few seconds or again after a period of minutes, sometimes only to fail again (Fig. 2), sometimes to resume its functions permanently. The tendency to recovery is more pronounced the smaller the dose of adrenalin, and, a point of great practical importance, the deeper the degree of anæsthesia. In the case of an injection being performed under artificial respiration the tendency to recovery is likewise increased.

The cessation of the heart's action from ventricular fibrillation occurring under the influence of chloroform is abrupt and complete. The sudden fall in the blood-pressure, which constitutes such a striking feature in many of the tracings reproduced, occurs in fact absolutely simultaneously with the onset of fibrillation. This was seen to be the case in simultaneous manometric and galvanometric curves in which corresponding points could be identified

with certainty. Moreover, the onset of a full period of fibrillation is unmistakeably and immediately evident to the naked eye when the heart is at the time exposed, and is readily enough differentiated visually from the complicated irregular action of the heart which precedes it. This fact was demonstrated by depressing a signal key on observing the onset of fibrillation in an exposed heart, the signal marks on the kymographic record being always found to correspond with the dips in the pressure curve ; such a kymographic record is shown in Fig. 2.

It is made certain in this way that momentary periods of ventricular fibrillation may occur, resulting in a sudden but slight fall of pressure only, for rapid recovery of the heart precludes a very low fall. Such short periods certainly may not be always easy to differentiate with the eye from the intermixed periods of multiple extrasystoles, although they are perfectly indicated on the manometer tracing, and I think that such an intermingled sequence of short but definite periods of fibrillation and tachycardias may possibly in some cases create an impression of transitional conditions : I am referring simply to my own special experiences, and I do not wish to infer that modified forms of fibrillation may not occur under some other conditions. For all practical purposes therefore I regard the cessation of the heart's action and the consequent fall of blood-pressure as a definite means of discriminating between fibrillating and non-fibrillating ventricles, and I do not, at least in respect of these chloroform experiments, regard the ventricles as truly fibrillating in any case in which the blood-pressure is sustained.

The occurrence of ventricular fibrillation may be confirmed by cutting open the chest and slitting up the pericardium as rapidly as possible after the fall of blood-pressure. The ventricles may then be found in the first or coarse stage of fibrillation, but if inspection be longer delayed the second stage may be encountered ; the ventricles are then found in a state of relaxation and exhibiting faint fibrillary twitchings, which may be only perceptible on close inspection of the region of the intraventricular septum. A test may be performed for the presence of true fibrillation, when otherwise doubtful, by firm rhythmic compression of the heart, for this tends to restore the initial, and more readily visible, stage of fibrillation. The auricles, if inspected at a sufficiently early stage, may be found actively fibrillating, but this condition soon passes off, and a feeble rhythmic beat supervenes which may continue for a very long time. If, as is usually the case, the animal dies under conditions of full vascular aeration, then the left auricle is bright red and the right purple in colour.

A precipitate fall of blood-pressure from a high or moderate pressure level under chloroform and in sequence to a stage of irregular tachycardia may be taken as invariably indicative of ventricular fibrillation. At first I systematically inspected the heart after syncope, whether induced by adrenalin or by any other means, and I *invariably* found the ventricles exhibiting fibrillary contractions. Latterly therefore I have not in every case confirmed the reaction in this way, as it is unnecessary, the sequence of
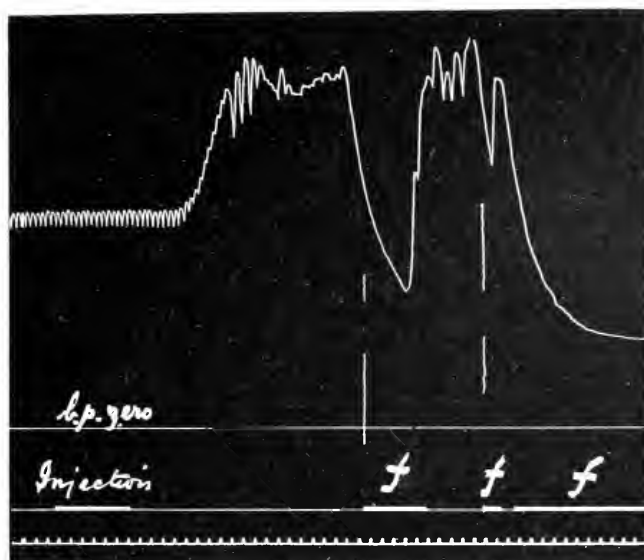
Fig. 2. × ¾. Ludwig manometer curve showing how periods of V.F. may be *observed* in the exposed heart and correspond to dips in the *recorded* blood-pressure curve. The signal marks f, f, f, were made by depressing the signal key when the ventricles were observed to pass into a condition of fibrillar contractions. These periods were definitely differentiated by inspection alone from the condition of multiple extrasystoles which preceded and succeeded them, and the signal marks are seen to synchronize with the deep dips in the blood-pressure curve. The chest wall and pericardium were laid open and artificial respiration maintained with 0·5% chloroform. Adrenalin 0·2 mgms. injected into the saphenous vein. Time in seconds.
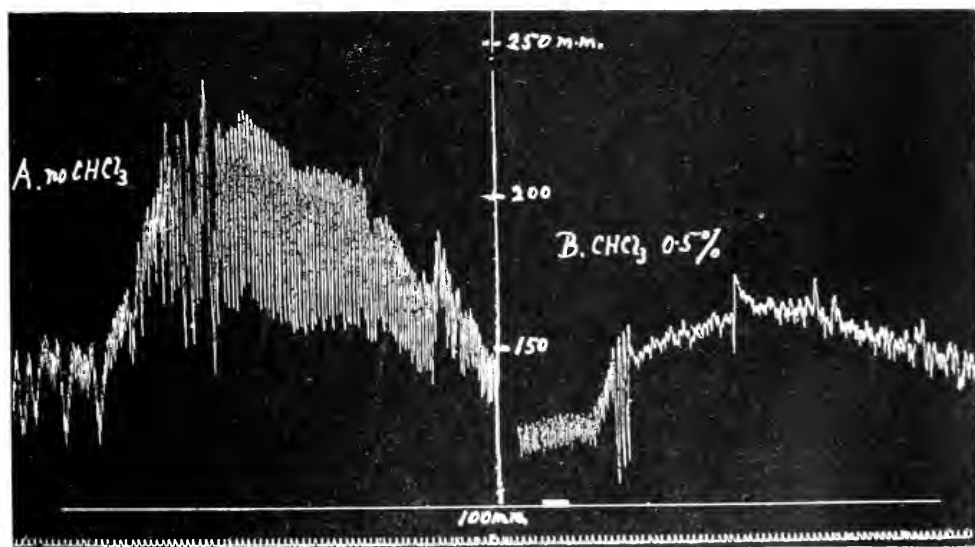
Fig. 3. × ⅓. Contrasted consecutive Ludwig curves from the same animal, showing the result of an intravenous injection of 0·065 mgms. of adrenalin. A. when not under chloroform, B. when under 0·5% chloroform. In A. the heart beat is slowed and regular, the initial intermissions being due to volitional movements. In B. the heart passes into a condition of multiple tachycardia. Cannula in crural artery. The abscissa line has been raised to the 100 mm. pressure level, and the vertical index represents higher pressures. Time in seconds.

events being absolutely diagnostic. I may add that I have never observed a sudden cardiac syncope in sequence to a regular heart beat in any of the experiments described in this paper.

A series of asphyxial gasps follow sudden cardiac syncope, and form a notable feature in death from ventricular fibrillation under chloroform. They demonstrate that the respiratory centre is active and not depressed by the action of the anæsthetic, and are more or less marked according as anæsthesia is deeper or lighter at the moment, and in the lighter degrees they are accompanied by a state of asphyxial spasm of the whole body ; desultory respiratory efforts may continue long after the failure of the heart. A tracing of this respiratory phenomenon as a result of adrenalin injection has elsewhere[14] been shown, and another example (Fig. 19) is given in the course of this paper to illustrate that a precisely similar result occurs as a consequence of ventricular fibrillation produced by other means. On recovery of the heart from fibrillation the respiration again recovers itself, and on recurrence of fibrillation the exaggerated phase is again repeated, and thus it may happen that the actual process at work may be somewhat obscured in the case of a death from ventricular fibrillation, in the absence of a graphic record of events.

(b)   Control experiments.

These were performed by injecting adrenalin into animals not under the influence of any anæsthetic, and subsequently repeating the injection after the administration of chloroform.

Two methods were employed :—

(i). Limited to a single experiment. The curves were taken from an intact animal by the method of Brooks,[2] and are shown in Fig. 3. The first curve, resulting from the injection of adrenalin* when the animal was not under the influence of any anæsthetic, is characterised by a retardation of the heart beat, which remains regular. There are intermissions in the first part of this curve, but I doubt if these are really due to single extrasystoles ; they are sufficiently explained by the animal happening to move at this moment—for the duration of the rest of the curve it remained perfectly quiescent. The second curve was taken after chloroform anæsthesia had been induced, the percentage being reduced to 0·5% at the time of the injection ; it is fairly typical of a chloroform tachycardia as registered by a mercury manometer, but this experiment proved to be an exceptional case, for the tachycardia did not terminate in fibrillation. The dose of adrenalin in each instance was 0·065 mgms.

(ii). The animal was rendered anæsthetic in the first place by pithing the cerebrum and subsequently put under chloroform. Five experiments of this kind were performed. Under such circumstances adrenalin causes a large rise of blood-pressure in the absence of chloroform, but even when employing

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* The injection was made under cocaine into the crural vein, which had been previously exposed in preparing the crural artery.

Fig. 4. × ¾. Contrasted Hürtle curves taken in sequence from the same animal; A. rendered anæsthetic by pithing the cerebral hemispheres and not under the influence of chloroform; B. under 0·5% chloroform. The curves have been superimposed for convenience of contrast, the signal line being adjusted to serve as abscissa line to both curves. The vagi had been previously cut and large doses (0·2 mgms.) of adrenalin were injected. The signal mark serves to indicate the moment of injection in both cases.

In A., the heart beat is accelerated but remains regular. In B., the heart passes into an irregular tachycardia with a well marked period of fibrillation toward the end of tracing.

The numbers inscribed indicate mean blood pressure values registered by means of a damped Ludwig manometer (not shown).

Artificial respiration. Time in seconds.

abnormally large doses, I have not observed any trace of irregularities. The pulse rate under such conditions may be affected in either direction (out of five experiments acceleration occurred in three and retardation in two), but otherwise the beat is unaffected and the tracing is generally remarkable for its perfect regularity. When, however, chloroform is administered to an animal treated in this fashion, then, although adrenalin does not invoke a permanent fibrillation of the ventricles,* yet the usual sequence of intense irregularities, often with momentary periods of fibrillation, is brought about. Paired observations of this nature are illustrated in Fig. 4 and 5. In the experiment from which Fig. 4 was taken the vagi had been cut and large doses (0·2 mgms.) injected in order to obtain a full effect ; in the curve taken without chloroform the beat was rapid both before and after the injection, but slightly accelerated after ; the beats were powerful and normal beats, as was confirmed by reference to the simultaneous damped mercury manometer curve (not shown in the figure) in which every beat was well defined, with well-marked respiratory curves and without a trace of the irregular dips in pressure which are so characteristic of extrasystolic tachycardias. In Fig. 5 are shown a contrasted pair of curves registered by the undamped mercury manometer, the vagi being uncut and the usual small doses of adrenalin being administered.

The foregoing experiments clearly demonstrate that adrenalin has not any innate power of producing ventricular irregularities, but that it acts as an *exciting cause only* when the heart is rendered sensitive by chloroform. This statement is at variance with the observations of Kahn,[11] which have been generally regarded as indicating that multiple tachycardias are a frequent and normal sequence of adrenalin injections (*cf.* electrocardiogram No. 16 in his paper), but Kahn's experiments are vitiated by reason of his experiments being performed with animals deeply under a general anæsthetic, a mixture containing chloroform (chloroform 9, ether 30, petroleum ether 3), and this fact brings his observations into conformity with my own.

(c) *The cardiac action of adrenalin.*

The action of adrenalin on the heart is a local one and not induced through central nervous agency. This was proved by isolating the heart from all nervous connections. The isolation was performed very thoroughly by extirpating the stellate ganglia or by section of their cardiac branches, together with section of the vago-sympathetic trunks in the neck ; the spinal cord was destroyed in addition in some instances, in one case the bulb also. Six experiments were performed and in five of them the heart fibrillated. The following experiment will serve as an example.

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* This has since been attributed to a stimulation of the vagal centres by the act of pithing and by the subsequent high intracranial pressure.

Experiment, August the 15*th,* 1912. Both stellate ganglia excised at a previous operation. Vagi cut. Spinal cord destroyed by passing a stylet down the vertebral canal under artificial respiration.

The injection of 0·065 mgms. of adrenalin chloride into a saphenous vein under 0·5 per cent. chloroform induced V. F. in 22 seconds

In Fig. 6 is shown a tracing of a similar experiment. The curve is somewhat unusual in connection with adrenalin in showing an early period of what are, apparently, slowed beats, but which close inspection of the original curve shows to be conditioned by a bigeminy due to extrasystoles.
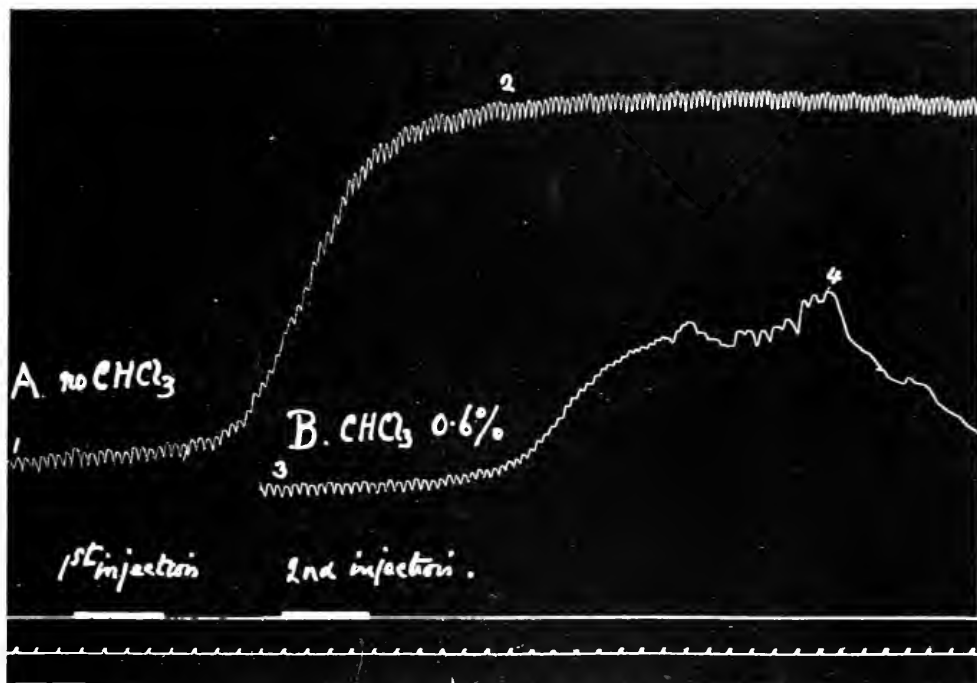
Fig. 5. × ¾. An experiment performed under similar conditions to that described in the preceding figure. Ludwig manometer employed in this case. The vagi were not cut, and ordinary doses (0·065 mgms.) of adrenalin injected. The signal line had been adjusted to serve as the abscissa to both pressure curves. The numbers serve as a reference to blood-pressure levels as follows : (1) = 74 mm. ; (2) = 200 mm. ; (3) = 64 mm. ; (4) = 130 mm.

(d) *The reaction in chloroformed dogs.*

The reaction in dogs is similar to that in cats, but a larger dose of adrenalin is apparently necessary, *e.g.,* 0·13 mgms. The tachycardia produced, so far as I have observed it, is not so rapid as in the case of cats.

(e) *The adrenalin reaction in the chloroformed human subject.*

A communication[18] in regard to this matter was recently read before the British Medical Association, and it was therein shown that fatalities have occurred from the ill-advised use of adrenalin for surgical purposes and for the treatment of shock in patients under chloroform. It was shown, moreover,
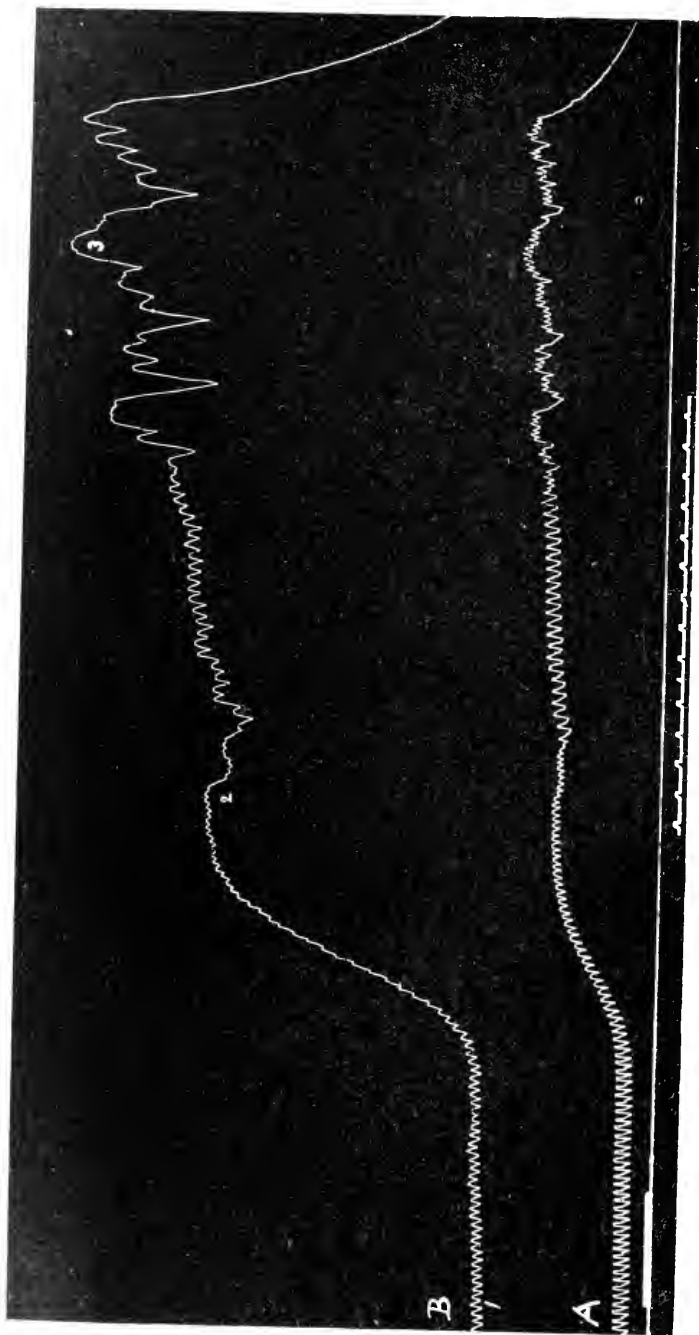
Fig. 6. × ⅔. Simultaneous Hürtle (A) and damped Ludwig (B) curves showing the action of a large dose (0·2 mgms.) of adrenalin in a cat under chloroform in which the heart had been isolated from central nervous influences. The vago-sympathetic nerve trunks were cut in neck, the cardiac branches of both stellate ganglia were cut and the spinal cord was destroyed by passing a stylet down the vertebral canal. Artificial respiration with 0·5% chloroform. The signal mark represents the moment of injection. The signal line has been adjusted to serve as abscissa line to both curves. The heart is regular before injection. A rise of blood-pressure with cardiac acceleration is the first effect of the injection. The blood-pressure falls with the first onset of cardiac irregularity (2). The heart then passes into a phase of slowed action, the slowing being seen on careful inspection to be due to periodic extrasystoles. The next phase is one of a very irregular tachycardia of about 360 beats per minute, and finally the blood-pressure rapidly falls to zero as a result of ventricular fibrillation. The numbers denote blood-pressure levels as follows : (1) = 69 mm. ; (2) = 174 mm. ; (3) = 232 mm. Time marked in seconds.

that the anæsthesia was a light one at the time of the injection and that the mode of death was similar to that which occurs in cats under similar conditions.* The only difference noted was a pronounced tendency to recovery in the human subject.

A further fatality of this kind has been reported just recently (*Brit. med. Journ.*, 1913, I, 879). The following is a brief abstract :—

"The patient was a male aged 26, a well-developed and healthy man. Operation for deflected nasal septum."

"Anæsthesia was induced by chloroform given upon a Skinner's mask, and it was decided to inject some adrenalin into the nose subcutaneously. At the time of the injection anæsthesia was light (a brisk corneal reflex being obtainable), the pulse strong, and the patient's colour good. No more chloroform was given."

"About one minute after the injection the pulse suddenly became very rapid and then imperceptible ; at the same time the patient's colour became leaden grey and the pupils widely dilated. About three deep gasps were taken after the pulse had failed, and then respiration ceased."

II. The direct cardiac effect of excitation of the accelerator nerves.

If we dismiss the general pressor action of adrenalin from consideration and regard ventricular fibrillation as resulting from the excitory influence which adrenalin exerts upon the myoneural junction of the sympathetic nerve supply of the heart, then it is evident that confirmation of this view should be obtained by exciting these same junctions through ordinary physiological channels, *i.e.*, through the accelerator nerves themselves. Such an experimental procedure does in fact confirm this view of the action of adrenalin in a convincing and complete manner. A short note[16] has already appeared touching on this subject, but it requires some further reference here.

The experimental procedure adopted was as follows : The cat was anæsthetised in the usual way, care being taken to avoid any unnecessary excess of chloroform throughout. The right stellate ganglion was exposed by Anderson's dorsal operation between the heads of the first and second ribs and all its connections were divided with the exception of the two post-ganglionic cardiac nerves. A carotid artery was then prepared and connected with the manometer. The ganglion was caught up on electrodes hooked in between the cardiac branches, and was stimulated with a faradic current. The result of this stimulation upon the heart in the presence of a weak percentage of chloroform is almost precisely the same as that resulting from the injection of adrenalin, *i.e.*, the ventricles pass from a condition of regular rhythmic contraction into one of multiple arhythmic tachycardia terminating in ventricular fibrillation (Fig. 7 B). The onset of irregularities and of fibrillation may be very rapid, the latter may in fact occur within seven seconds from the commencement of the stimulation, but it is more frequently delayed for some 30 seconds.

TABLE I.

No.	Preparation of	Chloroform percentage	Excitation Coil at	Left Ganglion excited	Right Ganglion excited.
1.	Right ganglion	0·5	55 mm.*		V.F.
2.	Right ganglion.	0·5	100 mm.		V.F.
3.	Right ganglion and both vagi cut.	1·8	93 mm.		V.F. of 3 seconds duration.
4.	Right ganglion.	0·5	93 mm.		V.F.
5.	Right ganglion	0·5	100 mm.		V.F.
6.	Right ganglion.	0·5	93 mm.		Irregularities only.
7.	Right ganglion.	0·5	93 mm.		V.F. of 2 seconds duration
8.	Right ganglion.	0·5	93 mm.		V.F.
9.	Right ganglion.	1·0	70 mm.		V.F.
10.	Right ganglion.	0·5	100 mm.		Irregularities only.
11.	Right and left ganglia.	0·5	93 mm.	Slow tachycardia	Rapid tachycardia.
12.	Right and left ganglia.	1·5	55 mm.	No irregularity.	V.F.
13.	Left ganglion.	0·5	55 mm.	Slow irregularities.	
14.	Left ganglion.	0·5	100 mm.	V.F.	
15.	Left ganglion	0·5	75 mm.	Slight irregularity.	

* With the coil at 95 mm. the current was just too painful to be applied to the tongue.

The above table provides an abstract of the whole of my experiments upon excitation of the stellate ganglia, not precisely in the order of their performance, but grouped for purposes of tabulation. In many of them a number of excitations at higher percentages of vapour preceded those tabulated, but these were ineffectual in producing ventricular fibrillation.

The outstanding feature of this series of experiments is the frequent incidence of ventricular fibrillation from excitation of the right ganglion under low percentages of vapour. In Experiment No. 12 the percentage

indicated was 1·5%, but the animal was only moderately anæsthetised. In Experiment No. 3 fibrillation was obtained at 1·8%, the animal being apparently well under the anæsthetic, but in this case the vagi had been previously severed, a factor which must be taken into account. This heart recovered in three seconds. In all other instances on stimulation of the right ganglion at 2% or thereabouts, the heart either remained regular, or, as was more frequently the case, assumed a condition of a rapid irregular tachycardia, with possibly a mere flicker of fibrillation, but never coming to a complete standstill (Fig. 7 A).
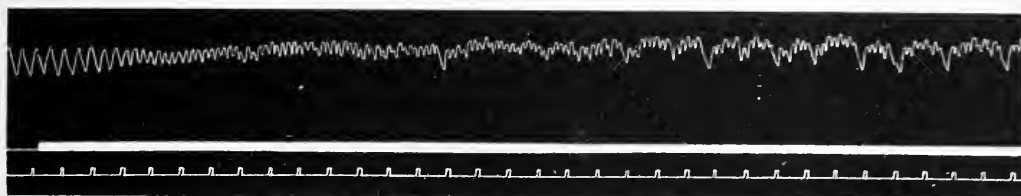
(A)
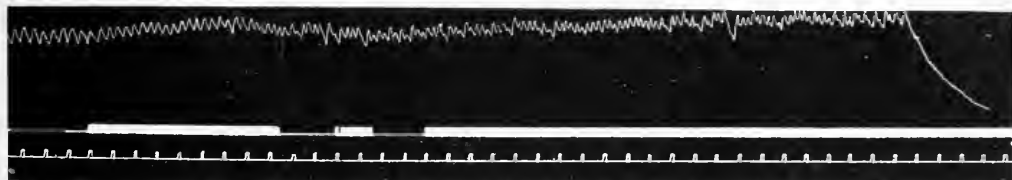
(B)
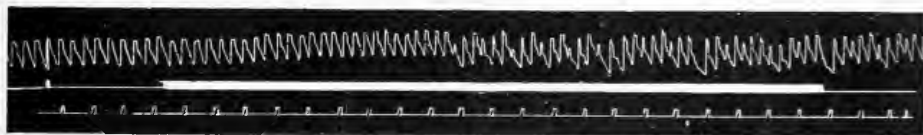
(C)

Fig. 7. Excitation of a stellate ganglion under chloroform, all nervous connections of the ganglion, with the exception of the cardiac branches, having been cut. The tracings were not taken from the same individual. Hürtle manometer. The signal line serves as abscissa in each case. The excitation was faradic, with the coil at 95 mm. Time marked in seconds.

    A. Right ganglion excited under 2% chloroform. A multiple tachycardia is induced but the ventricles do not fibrillate.

    B. Right ganglion excited under 0·5% chloroform. A similar tachycardia is produced but terminating in ventricular fibrillation in 37 seconds.

    The gaps in the signal mark are due to temporary failure of the interrupter.

    C. Left ganglion excited under 0·5% chloroform. A tachycardia is induced, but it is of a less intense type than that seen on excitation of the right ganglion.

The result of stimulation of the left ganglion is dissimilar—rapid irregularities are seldom seen from this side, and the curve shown in Fig. 7 C is typical of the result which is generally obtained.* In experiment No. 14 alone was fibrillation produced, the heart in this case being very irregular before the excitation was made.

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* Possibly this difference is subject to a purely anatomical explanation, for the left stellate ganglion is smaller than that on the right side in the cat.

Experiment No. 3 may be specially cited as showing that the stimulation of the heart through the accelerator nerves exercises its effect upon the chloroformed heart through its own influence alone and independently of any relation to a concurrent vagus tonus ; in fact the previous removal of vagal influence appears to favour the onset of ventricular fibrillation at a higher grade of chloroform anæsthesia than is usual. The details of this experiment are as follows :—

TABLE II.

CHLOROFORM.		PULSE RATE.	REMARKS.
2%		84	Beat regular.
2%	Vagi cut.	180	Beat regular.
1·8%	Stimulation to right stellate, coil at 100 mm.	320	Tachycardia culminating in V.F. of 3 seconds' duration.

Many workers have sought to obtain ventricular fibrillation through accelerator action. Of these the most successful, hitherto, have been Rothberger and Winterberg,[25] who obtained abnormal beats, in dogs subjected to the narcotic influence of morphia and curari, by combined vagal and accelerator stimulations, and in rare instances they obtained ventricular fibrillation. In a further series of experiments on dogs under ether, and further submitted to the influence of moderate doses of barium chloride, they invariably obtained complex ventricular tachycardias on stimulating the left accelerators, but they do not appear to have attained any greater measure of success in respect of producing ventricular fibrillation in this series than they did in their former series.

The action of chloroform, described above, of rendering the heart irritable and causing it to react in an abnormal fashion to accelerator influences is thus far unique in respect of its potency.

III. CARDIAC EFFECTS ARISING AS A REFLEX FROM SENSORY STIMULATION.

Bearing in mind the foregoing demonstration of ventricular tachycardias and fibrillation excited through the agency of the accelerator nerves, it might be anticipated that similar effects would be induced through reflex mechanisms by the excitation of sensory nerves ; as a matter of fact, every cardiac effect previously described may be reproduced in such a manner. The heart responds very readily to sensory stimuli by passing into an irregular condition just as it does under the influence of adrenalin or of accelerator excitation ; and in just the same way the reaction is modified by the depth of the anæsthesia. At 2% or over the onset of irregularities is uncertain, and if they do appear they may exhibit various degrees of intensity, but they never pass into ventricular fibrillation. Under lighter degrees of anæsthesia, 1%
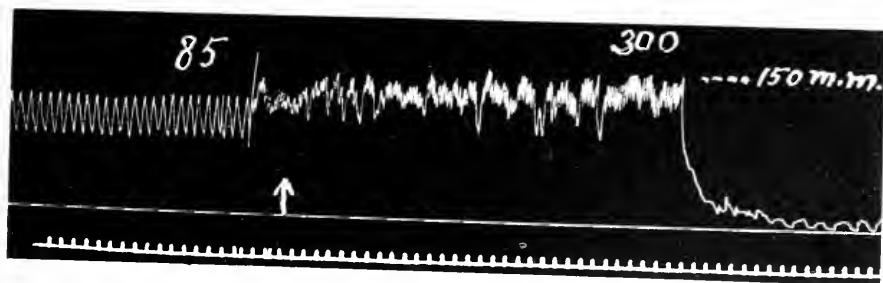
Fig. 8. Hürtle curve showing tachycardia and subsequent V.F. induced by cutting a sciatic nerve. The first part of the tracing shows a regular slow beat (bigeminal ?) occurring under a moderate degree of anæsthesia, percentage not measured. The sciatic nerve was cut with a pair of scissors, whilst the drum was stationary, at the vertical line. The mechanical excitation caused a reflex stimulation of the heart and the consequent onset of an irregular tachycardia. The chloroform was removed at the arrow mark, and 30 seconds after this the blood-pressure fell from 150 mm. to zero as the result of ventricular fibrillation. The blood-pressure during the regular beat was 114 mm., the lowest pressure during the experiment, showing that the heart was not at any time unduly depressed by chloroform. The blood-pressure was registered as usual by simultaneous Ludwig records (not shown). The undulations seen at the end of the curve after fibrillation were caused by the terminal asphyxial gasps. The numbers above the curve represent the rate of heart beat per minute. Time marked in seconds.
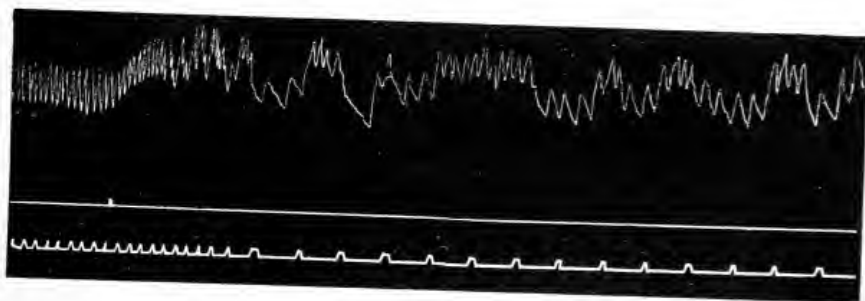
Fig. 8a. Hürtle curve showing the transition from a regular to an irregular beat arising from cutting a sciatic nerve with a pair of scissors. The signal mark indicates the moment of section. The signal line represents the Hürtle abscissa. Time in seconds. Rate of kymograph increased to analyse irregularities.
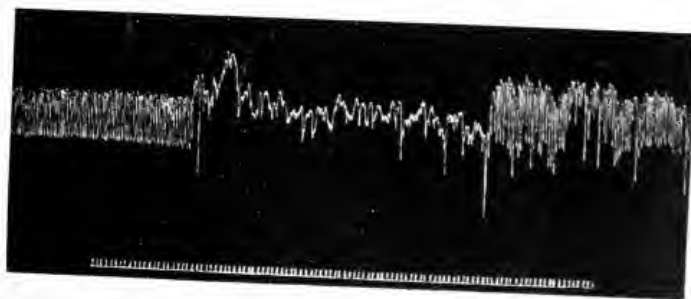

Fig. 9. Ludwig curve showing the reflex cardiac effect of applying ammonia vapour to the nostrils of a cat not long under chloroform. Strength of chloroform vapour = 1%. The time line has been raised to the 75 mm level. Time marked in seconds.

Fig. 10.   Hürtle curve showing the effect of cutting the sciatic nerve (2) and stimulation of the nerve (4) in a cat under light chloroform anæsthesia. The vagi were previously cut, and the heart was exhibiting an irregular tachycardia under 1% chloroform.   At (1) the chloroform had been taken off, and 0·5% vapour was given again at (3), just before the sciatic was stimulated.   The mechanical excitation of section of the nerve sends the blood-pressure up from 120 to 140 mm., makes the heart more irregular, and in 32 seconds causes V.F. with recovery in 3 seconds.   Faradic excitation of the nerves causes complete V.F. at a final blood-pressure of 154 mm.   This cat made a complete recovery about 60 seconds after fibrillation.

Fig. 11.   × ³⁄₄. (Redrawn). Ludwig curve shows V.F. resulting from excitation of a median nerve by a faradic current with coil at 100 mm. Chloroform 0·5%.   The heart recovers after about 60 seconds with a slow and regular beat, relapsing into a tachycardia and later into V.F.   A second recovery and final collapse occurred in a precisely similar fashion (not shown in the figure).   Artificial respiration. The signal line has been adjusted to the pressure zero.   Time marked in seconds.

or under, the irregularities occur with great constancy and may present forms of the most intense description. The modifying influence of the depth of anæsthesia is illustrated in Fig. 15 in curves *a* and *b*. (Although the preparation of this animal was unusual, the curves may be taken as fairly representative.)

The irregularities thus produced may, and generally do, disappear sooner or later on the cessation of the stimulation, or being once started they may persist almost indefinitely and even sometimes be intractable to control through increasing the percentage of chloroform ; or they may culminate in ventricular fibrillation if the anæsthesia be sufficiently light.

Fig. 8 and 10 illustrate the onset of ventricular fibrillation resulting from the mechanical stimulus of cutting the sciatic nerve with a pair of scissors, and Fig. 8a shows the transition from a regular beat to an irregular tachycardia from the same exciting cause.

The form of excitation adopted in most cases was that of faradic stimulation as lending itself to purposes of exact comparison, but in a fresh nerve mechanical excitation such as that of cutting or crushing, or even merely cleaning the nerve trunk, is even more active in the production of irregularities. It is not even necessary to resort to such severe measures, for excitation of sensory nerve endings such as may result from cutting the skin, or from applying an irritant, such as ammonia, to the nostrils, will often produce a similar result (Fig. 9).

It is evident, for these reasons, that all the preliminary preparations for an experiment such as exposure of the artery for connection with the manometer must be performed under a well-established chloroform anæsthesia, otherwise reflex irregularities are set up, which may be very persistent, and are generally undesirable.

The onset of the irregularities is frequently somewhat delayed as compared with the reaction time in the case of direct accelerator stimulation (although by no means invariably so), and it is a further very notable fact that after several consecutive stimulations, the reflex becomes obscured or even totally abolished ; even when the later stimulations are applied to another and fresh nerve this fatigue is still much more noticeable than that which sometimes follows consecutive stimulations of the stellate ganglia. These facts are no doubt the outcome of a depression of the activity of the reflex centres through the influence of the anæsthetic. Under these more involved conditions it is not surprising that the most intense form of ventricular irregularity, *i.e.*, fibrillation, does not occur with any approach to the same frequency that it does as a result of a more direct stimulation of the heart, and that in fact its occurrence is a comparatively exceptional event. Thus out of my first series of some forty animals I only obtained ventricular fibrillation in six cases, and that not always as a permanent condition. These cases were as follows :—

1. Permanent V. F. resulted from pinching the central end of a sciatic nerve after the cessation of chloroform inhalation and 27 seconds from the commencement of excitation. The animal was still fairly under the influence of the anæsthetic when the nerve was excited and evinced no muscular reflex ; the heart was exhibiting irregularities previously to stimulation.

2.   (Fig. 10). In this animal both vagi were divided and the heart was in a state of persistent rapid tachycardia which had been originated by the act of cleaning the sciatic nerve. The chloroform (1%) was taken off and the left sciatic nerve was cut. In 32 seconds the ventricles fibrillated for 3 seconds and then recovered. Later 0·5% was administered and the sciatic stimulated with a faradic current ; complete V. F. ensued within ten seconds of the commencement of the excitation.

3.   Faradic excitation of a sciatic nerve under light anæsthesia, the heart beating regularly. An irregular tachycardia was produced passing in 13 seconds into V. F. of about 1 second duration.

4.   Permanent V. F. produced by a prolonged faradic excitation (about two minutes) of a sciatic nerve. The heart beat was regular just previous to excitation. Artificial respiration with 0·5% chloroform.

5.   Faradic excitation to a sciatic nerve under 1% chloroform, the heart beat being previously irregular. V. F. followed in 10 seconds. Recovery ensued after 6 seconds of fibrillation.

6.   (Fig. 11).   Faradic stimulation to a median nerve under 0·5% chloroform. The heart was irregular as a result of previous stimulations. Complete V. F., which persisted for about 60 seconds and was followed by recovery and again a further and final relapse.

In another and later series of eight animals the sciatic nerve was in four cases stimulated both before and after cutting the vagi, in the remaining four the vagi being left intact throughout. I obtained complete ventricular fibrillation with uncut vagi in one case, and in one other case with cut vagi. In both cases the heart was irregular before stimulation and in both the chloroform was of 0·5% strength.

The operation for exposure of the splanchnic nerves in the lumbar region is somewhat more severe than that for exposure of the sciatics, yet these nerves appear to be very sensitive in some individuals, and I obtained the high proportion of two cases of permanent V.F. out of a series of five animals in which the *central* end of a cut splanchnic nerve was excited by the faradic current. In both cases the heart was exhibiting irregularities before the nerve was stimulated, the chloroform in the one case being 0·8% and in the other 1·0%, in both cases anæsthesia was particularly well established, and there was no trace of spasmodic muscular reflex.

It may be inferred from the foregoing cases that ventricular fibrillation is more liable to occur if the faradic excitation is applied at a time when the heart is already exhibiting irregularities. I think this may be more generally the case ; I have seen death occur with remarkable rapidity in several instances upon simply picking up a nerve for the purpose of placing it upon the electrodes, the heart being irregular at the moment, but of these instances I do not possess tracings.

In two of the foregoing ten cases of fibrillation, both the vagi had been previously divided—this is an important observation for two reasons : (1) it totally disposes of any suggestion that these effects are in any way connected with a reflex stimulation of the vagus centre ; (2) it disposes of any suggestion that the results may be connected with reflex inhibition of the vagal tonus. Whether reflex fibrillation is favoured by thus cutting out vagal influence I have not sufficient statistics from the foregoing experiments to show, but there is some reason, as will appear from subsequent experiment and considerations, to believe that it does so.*

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* Garrey[6] is strongly impressed with the view that vagus excitation tends to oppose the onset of fibrillation as a result of faradisation of the ventricles.

(a) *The paths of action of sensory reflexes.*

Many of the foregoing experiments were originally performed with a view to investigating a presumed relationship between the onset of cardiac
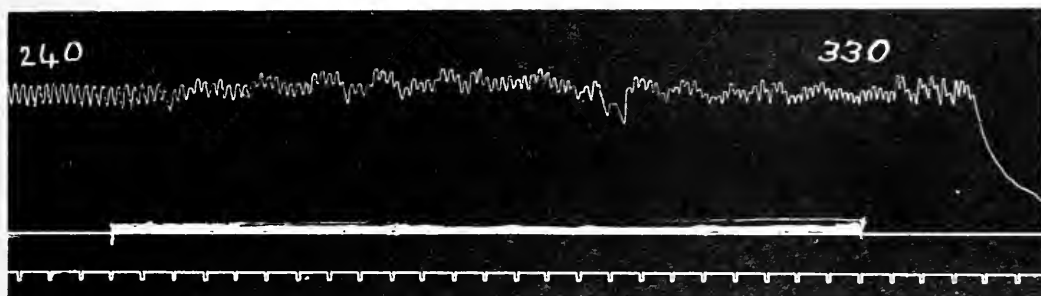

Fig. 12. Ventricular fibrillation caused by stimulation of a sciatic nerve in a cat in which both stellate ganglia had been extirpated six weeks previously. Chloroform 1%. Coil at 60 mm. The heart before excitation was regular, but rapid as a result of previous section of the vagi (rate 240 per minute). An irregular tachycardia appears within two seconds of the beginning of excitation and terminates in V.F. about four seconds after the cessation of the excitation. Blood-pressure just before V.F. = 146 mm. The numbers above the curve denote heart rate. Hürtle manometer. Time in seconds.
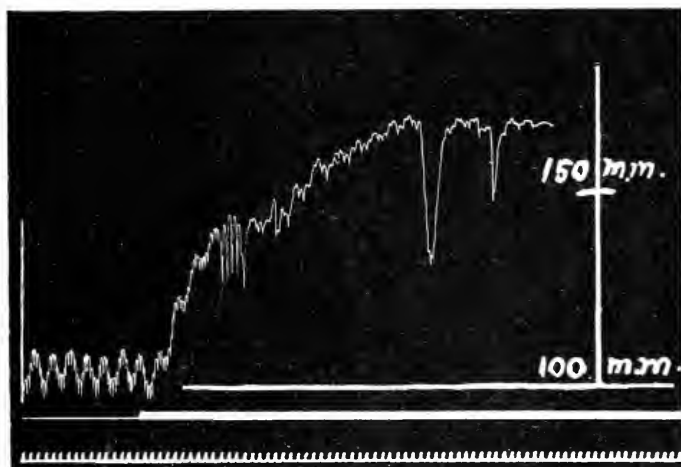
Fig. 13. Ludwig curve showing the result of stimulating the peripheral end of a cut splanchnic nerve under 1·2% chloroform. The blood-pressure rises abruptly as a result of vasoconstriction in the splanchnic area and partly as a result of secretory stimulation of the suprarenal body. In the first part of the rise the regularity of the heart beat is unaffected. The adrenalin effect commences as a series of single extrasystoles, which passes into a multiple tachycardia and temporary periods of V.F. This cat had previously received a dose of 0·13 mgms. of atropin sulphate (intravenous). The vertical scale indicates blood-pressure levels. Time marked in seconds.

irregularities and raised intra-cardiac tension dependent upon reflex vaso-constriction. The rise of blood-pressure resulting from sensory excitation is not very great under chloroform, but it is nevertheless generally quite evident. When I became aware of the action of the accelerator nerves I

sought further to test the influence of a raised intracardiac tension by severing the cardiac branches of both the stellate ganglia and thus exclude reflex accelerator action. In an experiment of this description the sciatic nerve was cut under 1% chloroform, the act of section causing the heart to pass from a regular to a bigeminal beat resulting from extrasystoles. The sciatic was then stimulated, and in 24 seconds the blood pressure having risen from 114 mm. to 134 mm., the bigeminal beat suddenly passed into an irregular tachycardia of 240 beats per minute with a fall of pressure to its earlier level.

This result was so suggestive that, in order to confirm it, I next undertook a series of experiments in which, for the purpose of excluding all possibility of accelerator action, both stellate ganglia were completely excised, the animals being allowed to survive and the final experiments performed some weeks afterwards when the cats had fully recovered from the effects of the operation.

Seven experiments of this kind were performed. In the final observations one of the hearts was exhibiting persistent irregularities from the commencement which could not be controlled and hence no satisfactory observations could be made. In one other a very few isolated extrasystoles only could be induced, but in the remaining five cats typical irregular conditions of the heart were produced by sciatic stimulation. Thus for instance :—

No. 4. Stellate ganglia extirpated three weeks previously. 1·9% chloroform. Cutting right sciatic excited a few bigeminal beats. Heart then became regular at 120 beats per minute. Sciatic stimulation, with coil at 70 mm. caused acceleration of the beat, the first extrasystole appearing 5 seconds from the commencement of stimulation ; an irregular tachycardia of 270 beats per minute then appeared.

No. 7. Stellate ganglia extirpated six weeks previously. The sciatic nerve was stimulated under 1% chloroform, which occasioned the onset of reflex irregularities, and these passed into ventricular fibrillation (Fig. 12) four seconds after cessation of the stimulation. The vagi had been previously cut.

These results appeared to afford evidence that a pressor action was indeed an exciting cause of ventricular irregularities under chloroform, and such a view was in conformity with observations I had previously made that excitation of the *peripheral* end of a cut splanchnic nerve in intact animals would throw the ventricles into a tachycardial condition ; in a single instance only did I observe fibrillation and that was of momentary duration only (Fig. 13) ; in these experiments there was no apparent source of reflex excitation of the heart through the accelerator nerves.

A complete explanation of these phenomena may be offered, however, quite apart from blood-pressure changes. The explanation is one which suggested itself as a possible cause of cardiac irregularities under chloroform when I first discovered the adrenalin reaction, but at the time I knew of nothing to support it. Since then papers have appeared by Cannon and de la Paz[3] on the secretion of adrenalin in strong emotional states, and by Elliott,[4] who has fully confirmed the fact that there exists a nervous control of the suprarenal secretion. This fact has evidently in the past given rise

to some confusion in physiological conclusions especially in relation to cardiac acceleration (*cf.* von Anrep[29]) and it had to be taken into consideration in relation to the matter under investigation, for the possibility had to be considered of adrenalin being secreted through a reflex nervous agency in sufficient quantity to determine abnormal ventricular contractions.

To test this matter further the following experiment was performed :—

Experiment, 23/8/12. Cat. Stellate ganglia excised five weeks previously.

Both splanchnic nerves exposed in the thorax under artificial respiration with chloroform. The nerves were cut and the peripheral ends ligatured separately. The left suprarenal gland was then excised by the lumbar route of operation. The peripheral ends of the splanchnic nerves were stimulated alternately with the same strength of faradic current (coil at 3,000 Kronecker, 5·4 volts current).

The following table gives an account of the consecutive procedures.

TABLE III.

Chloroform	Splanchnic Stimulation	Pulse Rate		Heart rhythm.
		before stimulation	after stimulation	
0·6%	Left	120	120	Regular before and after stimulation.
0·6%	Right	120	180	Regular before, irregular after stimulation.
0·6%	Right	120	240	Regular before, irregular after stimulation.
0·8%	Right suprarenal excised.			
0·8%	Left	150	150	Regular before and after stimulation.
0·8%	Right	135	135	Regular before and after stimulation.

This experiment is illustrated in Fig. 14 ; it affords evidence that a nervous influence will stimulate a suprarenal body to secrete sufficient adrenalin to excite a typical ventricular tachycardia under chloroform. The occurrence of irregularities in an animal subjected to such extensive dissection is especially significant, and it may be taken therefore as certain that the irregularities previously observed on stimulation of the peripheral end of a cut splanchnic nerve were in reality conditioned by the enhanced secretory activity of the suprarenal bodies, and that it is unnecessary to consider the co-existing pressor effect in this relation. So also an explanation is afforded of the reflex cardiac reaction from sensory stimulation in animals deprived of their stellate ganglia ; the reaction cannot be a direct reflex nervous action on the heart, but the heart is affected through the extra adrenalin secreted by reason of the reflex sympathetic stimulation of the suprarenal bodies. This reflex secretory effect has been directly demonstrated in other ways by Elliott and by von Anrep.

Having established the foregoing point it became necessary to re-investigate the function of the accelerator mechanism when excited by sensory excitation after excluding the adjuvant action of suprarenal secretion.

Attempts were made to isolate the suprarenal bodies from nervous influences by severing their splanchnic nerve supply, but, as I was never quite satisfied that all the sympathetic connections were dealt with, I preferred to rely only on experiments in which both glands had been extirpated. Five experiments were performed in which both glands were removed ; in two of these excitation of the sciatic nerve, both by cutting and by faradic excitation, produced ventricular irregularity of a moderately high grade, the highest pulse rates noted being 240 and 270 respectively. In the three other cats the splanchnic nerve was stimulated in continuity ; in one very little change in the beat was produced, in the second the heart was exhibiting a tachycardia from the commencement and hence the results were obscured ; in the third cat the heart was likewise irregular from the first, and in this case a strong splanchnic stimulation (coil at 30 mm.) sent up the rate of beat from 225 to 300 per min. and caused permanent ventricular fibrillation in 20 seconds.

In order to avoid the fatigue and shock of the double operation, in one other cat the right suprarenal was previously extirpated, the left gland alone being removed at the time of the experiment. This experiment is illustrated in Fig. 15 and described as follows :—

Experiment, 18/1/13. Left suprarenal extirpated on 3/1/13. Right suprarenal excised and right sciatic cut under 1·7% chloroform.

TABLE IV.

CHLOROFORM.	STIMULATION COIL AT	HEART BEAT	
		BEFORE STIMULATION.	AFTER STIMULATION.
1·7%	90 mm.	130 per min., regular	140 per min., regular.
0·5%	90 mm.	180 per min., regular	280 per min., irregular.
0·5%	50 mm.	240 per min., irregular	300 per min., V.F. in 20 seconds.

It is thus certain that all the reflex cardiac effects produced in the intact animal by sensory stimulation may be reproduced in an animal deprived of its suprarenal glands, that is to say, the reflex is equally active apart from any adjuvant secretory activity of the suprarenal glands. Thus, in the absence of any other unrecognised factor, sensory stimulations under chloroform may be said to effect the onset of cardiac irregularities by a dual agency ; *i.e.* (1) by reflex stimulation of the heart through the cardiac nerves, (2) by reflex stimulation of the suprarenal glands. Possibly both of these factors are capable of producing ventricular fibrillation individually, and it is difficult to say which plays the greater part ; it is known, however, that direct excitation of the cardiac nerves is far more potent in this respect than stimulation of the splanchnic nerves, and it may be inferred therefore that the former is the more frequent actual determining cause of complete ventricular fibrillation from reflex stimuli.

If sensory-cardiac reflexes under chloroform operate along these two paths alone, then no irregularities should appear on exciting a sensory nerve in cats in which both accelerator and suprarenal influences have been excluded. Such experiments have been attempted, but present considerable technical difficulties ; in the first place the stellate ganglia must be excised and the animals allowed to recover ; at a subsequent operation the suprarenal influence is cut off, and the animal again allowed to recover. When quite strong again, the experiment is performed. In one series of experiments of this nature I severed the splanchnic nerves on both sides at the second operation, and any obvious and accessible supplementary rami of the
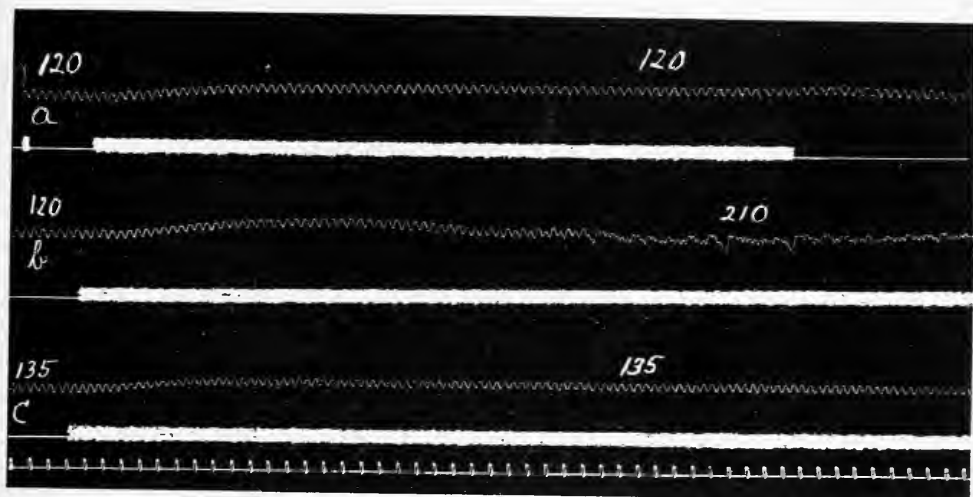
Fig. 14. × ⅔. Stimulation of the peripheral ends of cut splanchnic nerves. Coil at 3,000 Kronecker, 5·4 volts. Hürtle manometer.

A. Chloroform 0·5%. Left suprarenal extirpated, left splanchnic stimulated. The blood-pressure rises from vasoconstriction, but the heart beat is unaffected.

B. Chloroform 0·5%. Right suprarenal *in situ*, right splanchnic stimulated. The heart passes into an irregular tachycardia from increased secretory activity of the right suprarenal body.

C. Chloroform 0·8%. Right suprarenal extirpated, stimulation of the right splanchnic nerve. As in curve (a) the heart is now unaffected. The signal line in each case adjusted as abscissa. Time marked in seconds. The numbers above the curves indicate rate of heart beat. The splanchnic nerves had been exposed in the thorax and the respiration maintained by artificial means.

sympathetic system passing to the semilunar ganglia or suprarenals. In nearly all these experiments I obtained an actively irregular condition of the heart from sensory stimulations, but, as I have already observed, such a method of isolating the suprarenals is unsatisfactory—in fact, I invariably found at the *post-mortem* examination some accessory fibres which came off below the splanchnics, or even a splanchnic branch, remaining uncut ; in view of the extensive nervous plexus (Reighard and Jennings[24]) around the suprarenals the possibility of a reflex secretory effect could not be excluded with certainty.

In two further cats, therefore, I adopted the method of excising the suprarenals themselves ; this was done in two stages, as described in a former relation, and in both these instances distinct acceleration and irregularities were caused by stimulations of a sciatic nerve, and this both before and after section of the vagi.   In both of these cases, however, groups of ganglion cells were subsequently found in the regenerated tissues at the seat of the operation for excision of the stellate ganglia, and in view of this fact I think it is inadvisable to draw any definite conclusions or even to discuss these experiments until they have been more completely confirmed or negatived.*

Apart from all theoretical consideration of these lines of action a matter of outstanding practical importance has been conclusively demonstrated in this section, viz., *that a sensory stimulation under light chloroform anæsthesia may, through one or more reflex mechanisms, throw the ventricles of the heart into a condition of permanent and fatal fibrillation, or may initiate irregularities which may terminate later in ventricular fibrillation.   Under fully established chloroform anæsthesia such an event never happens.*

(b)   Reflex cardiac syncope in the chloroformed human subject.

It cannot be doubted that a similar reaction to that described above may occur in the human subject.   The adrenalin tachycardias and death occur in the chloroformed human subject, and there is no reason to question that man is similarly sensitive to sensory stimulations.   The annals of fatalities under chloroform teem with references to sudden and fatal syncope on the first touch of the surgeon's knife or during the earliest stages of an operation, just as the more intense effects are more readily obtained experimentally in recently anæsthetised and vigorous animals.   A large proportion of these fatalities occur in the course of trivial operations under chloroform in which, to save unnecessary subsequent discomfort, the minimum amount of chloroform is administered.

Unfortunately there are few absolutely precise records of the events accompanying death under chloroform in man ; naturally this is not a fitting moment for making scientific notes of pulse and respiration, and accounts written subsequently are generally confused, especially in regard to the time relation of events.   Here and there, however, clear descriptions may be found ; to illustrate my point I will confine myself to a single striking case described by Dr. Alex. Wilson, Senior Anæsthetist to the Manchester Royal Infirmary :—

CASE 6.   The patient, a girl of fifteen years of age, was operated on for *genu valgum* by Macewen's method.   Chloroform was given on lint ; she took it well, the operation was performed, and the splint in process of being put on.   At this stage, under the impression that all painful operative procedures were completed, the anæsthetic was discontinued.   The patient was then breathing quietly ; she had a good pulse and normal colour ; the pupils were slightly contracted, and the corneal reflex was present—in fact, she was coming out of the anæsthetic, but was *sufficiently insensible to bear ordinary manipulations or even incisions without feeling pain,* and

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* The possibility of a reflex stimulation of the pituitary body may be taken into consideration ; for the extract of this gland is capable of exciting ventricular irregularities.

was as well as anyone could wish her to be. At this instant the surgeon suddenly forcibly flexed the left knee, which was stiff owing to osteotomy having been performed on that side a few weeks previously. The adhesions gave way easily with a crunching sound, and the patient uttered a scarcely articulate cry, immediately became deadly pale, and began to breathe deeply. She passed at once into the following condition : The head was turned to one side, the face was deadly pale, the eyes were slightly open, the pupils were widely dilated, and she was taking deep inspirations, the air passing freely into the chest ; the muscles of the alae nasi were also acting, and the pulse was imperceptible at the wrist. The symptoms conveyed the impression that she had fainted. To drop the head, elevate the limbs, and apply hot sponges, &c., were the work of a moment. She continued to make strong respiratory efforts, and air was freely entering the lungs, but there was still no sign of the radial pulse. It appeared at first that the patient would probably recover—it seemed impossible that she could die with such active respiration ; but the breathing, without shading off in the least, suddenly ceased, and every effort to restore life failed. (*Lancet,* 1894, II, 1148.)

I have selected this illustration because it serves as a " type " case of ventricular fibrillation under chloroform from a reflex cardiac stimulation, corresponding in all essential details to those accompanying a death from cardiac stimulation by adrenalin in man and to those reflex syncopes observed and described by me in animals. The essential features are very graphically portrayed, viz., the light anæsthesia, the sensory stimulation, the sudden and complete heart failure, the continued and deepened respirations and the ultimate respiratory failure. It is not in every case of death from ventricular fibrillation that the attendant conditions are so well defined, or at least so carefully observed, and, in fact, under special conditions the special features are in some degree modified. A discussion of these modifications would be inappropriate in this paper : they require extended consideration and will be so considered from the clinical standpoint in a special paper bearing on this subject.* I am content for the moment to present a case which clearly confirms the occurrence of a reflex cardiac syncope in the human subject and which affords a parallel with the similar deaths which I have induced experimentally in animals.

Can a death of this description be ascribed to any cause other than ventricular fibrillation ?

It is absolutely certain that death in this particular instance was not conditioned by " over-dosage." There remains the prevalent idea that sudden death may result from the reflex inhibition of the heart through the vagi, and this view was adopted by the author of this report. But no vestige of direct experimental evidence can be adduced in support of such a view, despite the innumerable attempts to produce a fatal vagal reaction in the chloroformed animal. Permanent inhibition of the mammalian heart by reflex vagal action is unknown to experimental physiology, and although it has been considered that vagal inhibition might be fatal to a diseased heart, this is a matter of pure conjecture.† I have myself made an extended investigation[20] upon this supposed reflex action of the vagus, and found that although well marked vagal effects may be obtained through stimulation of the central end of the recurrent laryngeal nerve or of fibres running in the

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* Two additional cases of cardiac syncope under known percentages of chloroform are given in the Appendix to this paper. (Nos. 1 and 2.)

† Certain clinicians are now employing vagal compression as a test in cases of heart affections ; and they do so with impunity.

vagus trunk, yet even although the excitability of the vagus centre be raised by partial asphyxia, nothing approaching permanent stoppage of the heart's action is ever produced. I never observed any vagal reflex of practical significance as a result of stimulating sensory somatic nerves, and feel quite assured that no such thing ever happens, and it is evident that an *imagined* cause of death can no longer be accepted or even considered as an alternative to the *substantive* form of death through ventricular fibrillation which I have succeeded in demonstrating as a reflex phenomenon.

IV. The direct cardiac effect of section of the vagi.

Section of the vago-sympathetic trunks under light anæsthesia is one of the most effective measures for the production of typical chloroform
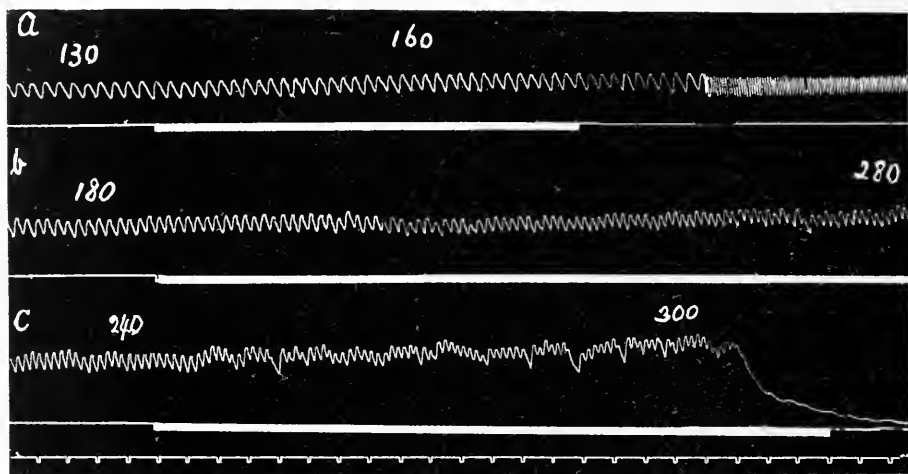

Fig. 15. × ⅔. Sciatic stimulations in a cat from which both suprarenal glands had been extirpated, the animal otherwise intact.
  a. Chloroform 1·7%. Coil at 90 mm. The heart beat accelerates from 130 to 160 per minute, but remains regular.
  b. Chloroform 0·5%. Coil at 90 mm. The heart beat passes into an irregular tachycardia, maximum rate 280.
  c. Chloroform 0·5%. Stronger stimulation, coil at 50 mm. Heart irregular when stimulated. The irregularities become more pronounced and terminate in V.F. Hürtle curves. Signal lines adjusted as abscissa. Time in seconds. The numbers indicate rates of heart beat.

tachycardias. Under deep anæsthesia, produced by 2% vapour or over, it sometimes happens that the heart accelerates only, remaining perfectly regular, but under these circumstances also pronounced irregularities may occur. Under light anæsthesia the irregularities invariably occur in sequence to vagotomy. Sometimes these eventually disappear, the heart then remaining permanently accelerated but regular ; sometimes they persist indefinitely, and in exceptional cases they terminate in ventricular fibrillation. These remarks apply to instances in which both vagi are cut ; section of one vagus alone does not, as a rule, give rise to the more complicated forms of irregularities, often to a bigeminus only.

I have had frequent occasion to perform vagotomy upon cats under chloroform, not in order to induce irregularities, but for the purpose of control experiments, and an endeavour was therefore generally made to suppress the irregularities by maintaining a full degree of anæsthesia. In such cases the ventricles never passed into fibrillation. I have, however, in addition to these, seven records of cases in which vagotomy was performed at 1% or at a lower strength of vapour, and it is probable that there were a few other unrecorded instances in which there was a negative result. In these seven recorded instances the heart was beating regularly before the vagi was cut. In two instances at 0·0% and in three at 0·5% the usual multiple tachycardia alone ensued. In the two remaining instances definite ventricular fibrillation occurred, in one instance temporarily, in the other permanently.

CASE 1. Fig. 16. Cat under 1% chloroform. Rate of beat = 90 per minute. Blood-pressure = 102 mm. On section of one vagus the blood-pressure rose a little and the rate was slightly accelerated. On section of the contralateral vagus the blood-pressure rapidly rose to 120 mm. and the beat was accelerated to 150 per minute. The heart then became progressively irregular, and the blood-pressure fell owing to cardiac insufficiency. A series of simple forms of irregularity were the first to appear (bigeminal action) which passed into higher grades of irregularity with short intervals of fibrillation and later a well-marked temporary cessation of the heart's action towards the end of the tracing occurred.

CASE 2. Cat under 0·5% chloroform. Every fourth beat an extrasystole, rate about 90 per minute. Blood-pressure = 100 mm. On cutting the vagi a multiple tachycardia ensued, the blood-pressure, after a preliminary fall on their first incidence, rising gradually to 146 mm. In 1½ minutes the ventricles passed into permanent fibrillation.
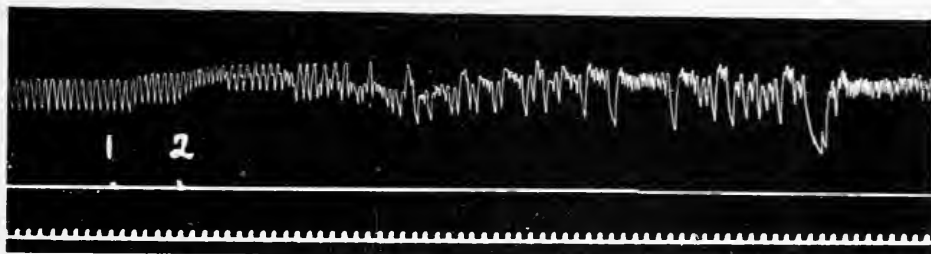

Fig. 16. Section of the vagi in a cat lightly anæsthetised by 0·5% chloroform. Previous to vagotomy the heart was beating regularly at a rate of 90 per minute. On cutting the vago-sympathetic nerve trunks in the neck (signal marks 1 and 2) the heart accelerates and the blood-pressure is forced up. The beat then by gradual stages becomes more and more irregular with momentary periods of ventricular fibrillation. Hürtle manometer. Natural respiration. Time marked in seconds. The signal line has been adjusted to the Hürtle abscissa.
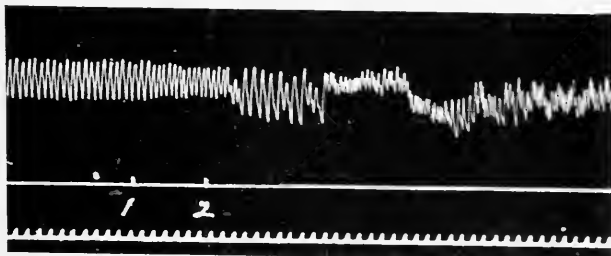

Fig. 16a. A similar experiment to the last, but in which the accelerator cardiac nerves were cut just previous to vagotomy. Chloroform 1·5%. Hürtle manometer.

The effect of exciting a vagus nerve is, as Gaskell[7] has shown, to depress all the cardiac functions. The effect of section of the vagus nerves is to cut out the tonic vagal influence on the heart, with the result of an increase in the cardiac functions, this increase being the equivalent of an excitation of the (so-called) accelerator nerves, which exert an exactly opposing influence to that of the vagi. Both section of the vagi and accelerator excitation, as is well known, increase the rate of rhythmic contraction of the heart, and also cause it to beat more strongly, so that the ventricular output is increased and the blood-pressure rises. These tendencies may be largely obscured under chloroform owing to the irritable condition of the heart and the consequent incidence of irregularities with loss of cardiac efficiency, but when observed apart from these abnormalities, the effect of section of the vagi is found to be precisely the same under chloroform as under other conditions. This fact is demonstrated under circumstances in which the heart is less irritable than usual, and in which as a consequence it remains regular after vagotomy, the manometric curve then presenting a perfect picture of increased cardiac efficiency. Thus :—

Experiment, January the 6th, 1912. (Fig. 17). Cat under 1·5% chloroform, anæsthesia well established. Heart beat regular at a rate of 165 per minute. Blood-pressure = 98 mm. On section of both vagi the rate rapidly increased to 240 and the pressure rose to 144 mm. in 22 seconds. The beat remained regular.
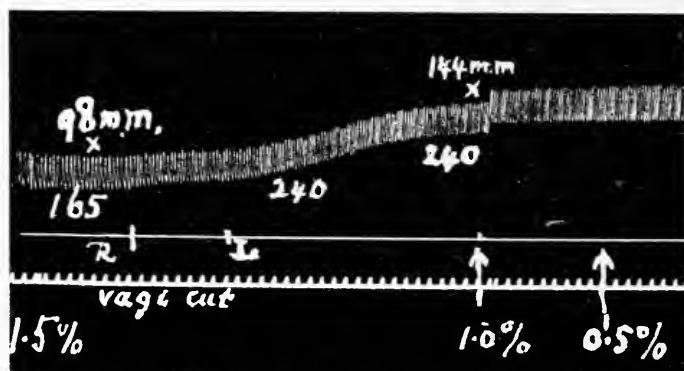

Fig. 17. Section of the vagi in a cat fully anæsthetised by 1·5% chloroform. The figures above the pressure curve indicate blood-pressure at the mark x, and those immediately below the curves denote rate of cardiac rhythm. The signal marks R and L denote section of the right and left vago-sympathetic nerve trunks respectively. The heart does not become irregular and hence the increased efficiency of the heart is fully represented by the rise of blood-pressure. A further rise takes place later as a result of reducing the anæsthetic at the arrow marks. Hürtle manometer. Signal line adjusted to serve as abscissa. Time marked in seconds.

A similar observation has been made on five other animals which were being subjected to artificial respiration, a condition which opposes the tendency of the heart to become irregular even in the presence of low percentages of chloroform. In these cases, likewise, on section of the vagi the heart remained regular but at once became accelerated, attaining generally a rate of 240 per minute or thereabouts. The blood-pressure was likewise affected, rising at once 10 or 20 mm., and subsequently and more gradually to a height which was in one instance as much as 50 mm. above the initial pressure.

The onset of ventricular irregularities as a consequence of vagal section may be explained in a manner which conforms with the explanations of my previously described experiments. Both adrenalin, and the so-called "accelerator" influences, whether direct or indirect, stimulate the heart to increased activity. By removing the tonic depressing influence of the vagal centres the heart is, in effect, *stimulated* in a precisely similar fashion. In short, it is a *stimulation* of the heart functions which is the determining cause of ventricular irregularities and fibrillation in a heart already rendered irritable by the action of chloroform.

If the above conclusions be correct, then increased vagal activity should have the effect of abolishing existing tachycardias. This is undoubtedly the case. I have frequently excited the peripheral end of a cut vagus nerve and have thereby succeeded in putting an end to a ventricular tachycardia. Such an experiment is illustrated in Fig. 18.
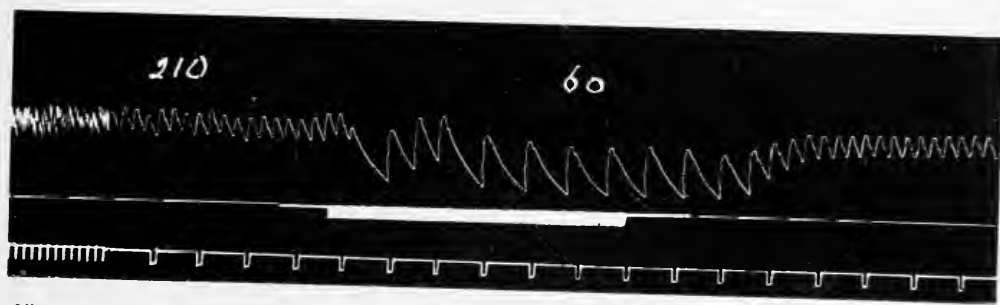

Fig. 18. The influence of vagal action upon the irregular heart. The peripheral end of a cut vagus nerve was stimulated by a faradic current with the coil at 90 mm. Before stimulation the heart was exhibiting an irregular tachycardia of 210 beats per minute. The irregular condition of the beat is more readily identified in that part of the tracing in which the kymograph moves at a slow rate. During excitation the heart is slowed to a regular beat of 60 per minute. Hürtle manometer. The signal line is adjusted to the abscissa. Time in seconds.

There is good reason to believe that an increase of vagal tone is responsible for a diminished liability to the *onset* of these cardiac irregularities, but I shall have occasion to deal with this point at greater length in my following paper.

A question of considerable interest is involved in the results of cutting the vagi. Does the cardiac stimulation and consequent irregularity arise as an automatic intracardiac increase of function, or does it arise from the now unrestrained, and hence augmented, action of the accelerator centres? This question appears to be fully answered by the following experiment :—

The cardiac accelerator nerves were exposed on both sides by Anderson's operation, and cut, and then the vagi were cut under 0·5% chloroform. The result was a procession of events almost exactly similar to that seen in Fig. 16, the heart passing by similar stages into a multiple tachycardia. (See Fig. 16a.) This result was confirmed in a later series of experiments on cats with denervated hearts, *i.e.*, on surviving cats in which the stellate ganglia

had been excised. The denervated heart is possibly even more sensitive than the normal heart, and in this series of nine experiments I met with a case of ventricular fibrillation from vagotomy under the exceptional condition of a 2% chloroform anæsthesia. Another case fibrillated under 1% chloroform vapour, and in the remaining seven the usual irregularities alone resulted. In these experiments the possibility of an exaggeration of the normal accelerator tone is excluded, and one is therefore led to conclude that ventricular abnormalities following section of the vagi under chloroform are not directly excited by a nervous impulse, but occur in sequence to a stimulation of the heart which is not the result of a direct nervous influence. In other words, the seat of origin of excitation of ventricular fibrillation after section of the vagi is intracardiac, and presumably, intramuscular.

The possibility of traumatic irritation (due to section) of afferent vagal fibres setting up a secretory reflex in the suprarenal bodies, and thus conditioning the irregularities in the foregoing experiments, may perhaps be considered. These afferent fibres are largely cardio-inhibitory and vaso-dilator in action, and such effects alone, so far as I have observed, result from the faradic excitation of the central ends of the severed vagi. It can, farther, be demonstrated that vagotomy gives rise to the same irregularities after excision of the suprarenal glands in addition to the stellate ganglia, and thus additional support is afforded to the view that they are purely intracardiac in origin. The following experiment illustrates this point :—

Experiment. Cat. Stellate ganglia excised seventeen days previously. Animal in fair condition. Both suprarenal glands excised, heart-beat regular, 120 per minute. The vagi were then cut under 1% chloroform and cardiac irregularities followed in twenty seconds.

Section of the vagi is an experiment which has no direct clinical counter-part. There does, however, exist a possible physiological parallel in a diminution of the normal vagal tone through reflex inhibition of the vagus centres, a subject which has been considered at some length by Reid Hunt.[10] Whether this may be an adjuvant cause of ventricular irregularities I cannot say, but inasmuch as I have obtained positive results in all my control experiments with the vagi previously cut, it does not appear to be a matter deserving immediate further investigation.

V. Ventricular fibrillation of apparently spontaneous origin.

In the foregoing section I have described how reflex stimulation of the heart, such as results from operative procedures, may produce ventricular fibrillation under conditions of light chloroform anæsthesia. I have now to describe how ventricular fibrillation likewise occurs (1) during the induction stage, when the heart has not come fully under the influence of the chloroform, and (2) during the recovery stage, when the heart is being released from the full influence of the chloroform. In these stages ventricular fibrillation may be apparently spontaneous in origin, in so far as there is not any source of reflex cardiac stimulation arising from operative manipulations.
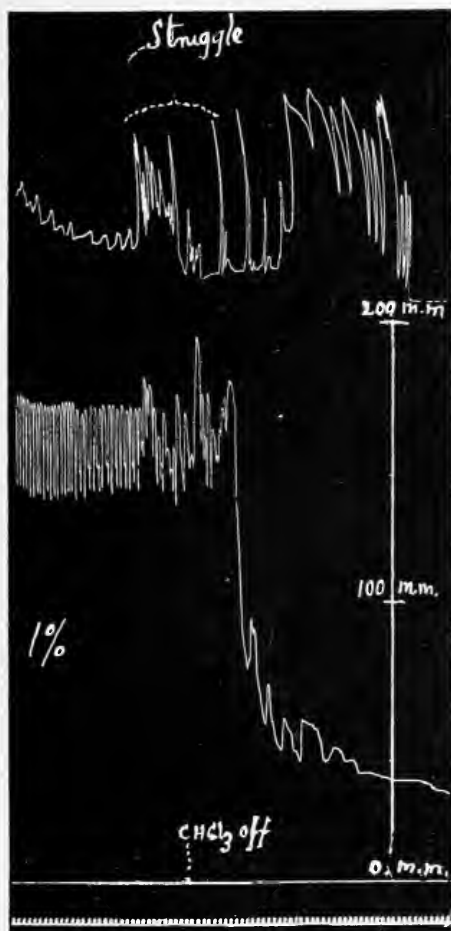
Fig. 19. × ¾. Ventricular fibrillation caused by struggling during the induction period. Cat prepared by Brooks' method. Cannula in crural artery. Upper curve, respiratory. This shows a declination in its first portion caused by a leak in the recording apparatus. Lower curve, blood-pressure. Ludwig manometer.

Anæsthesia induced by 1·5% chloroform, then 2%, then reversion to 1%, when animal was roused to a state of excitement and struggled freely. The heart became very irregular, the chloroform was entirely removed, and the ventricles fibrillated a few seconds later. The fluctuations in the blood-pressure during struggling are mainly mechanical, and the small irregular beats are almost obscured in the reproduction. The final fluctuations at the foot of the pressure curve are caused by the powerful asphyxial respiratory gasps, which are delineated in the respiration curve. The heart was inspected immediately on the cessation of respiration. The ventricles were found in a state of coarse fibrillation. The auricles were beating faintly, the left auricle containing blood which was darker than usual after V.F..

(*a*) *Observations without recording apparatus.*

A brief account of ventricular fibrillation occurring in the induction stage of chloroform anæsthesia in cats, and of the definite ways in which it is brought about, has already been published.[15] Eighteen cases of sudden death during the induction of anæsthesia had been noted at the time, and several more of an exactly similar nature have been since observed. Many of these cases were the result of a pure accident at a time when I was unaware of the proper principles of administration, and others more recently have been the result of set procedures in the endeavour to reproduce them. These deaths are of a remarkably sudden nature, the animal is obviously not overdosed, yet the respiration stops suddenly from no apparent cause, the heart is found to have ceased beating and in the generality of cases no measures, however prompt or energetic, will avail to restore the animal.

If the animal were being carefully observed shortly before the respirations ceased a phase of exaggerated respiration would be noted, often of itself sufficient to attract attention, and sometimes taking the form of powerful expiratory spasms, accompanied by loud phonation, the whole body at the same time twisting in a convulsion. Sometimes violent struggling, evidently the volitional efforts of a semi-conscious animal, would precede the terminal phase of exaggerated respiration. This form of death in animals has been recognised and even carefully described, and the cause of

death ascribed to an excessive intake of chloroform as a result of the abnormal respiratory amplitude. There is an element of unconscious irony in this attempt to exploit a physiological theory upon the body of a dead animal, for the animal is indubitably dead before the exaggerated respirations appear; they are but the physiological sequence of a rapid and complete circulatory failure, to which reference has already been made in Section I (*a*) of this paper (see Fig. 19). These asphyxial gasps are an almost invariable sequence of ventricular fibrillation from any cause, but in some cases they are modified by the condition of the animal or the degree of anæsthesia; thus the respirations, though continuing after cardiac syncope, may not be exaggerated, or they may even, though long drawn, be diminished in amplitude.

Although when, some years ago, I first observed this form of death I did not recognise its cause, I was convinced it did not result from an excess of vapour. The anæsthesia was at that time induced by placing a bag made of loosely woven fabric on the animal's muzzle and dropping chloroform upon it. The process was carried out with precision and with a careful progression so that I was in this way enabled to chloroform cats without any excitement and without any assistance and to avoid over-dosage with certainty. From my knowledge of the evaporation of chloroform under such conditions I was convinced that at no stage was an excessive percentage of chloroform administered.

At a later stage I induced anæsthesia by means of the bag and drop bottle, and discarding this when the animal was fairly anæsthetised I continued with the *ad plenum* method of administration with a 2% or lower strength of vapour. An interval, during which the cat was not inhaling an anæsthetic, was thus introduced.

Subsequently anæsthesia was habitually induced from the beginning by the *ad plenum* method, commencing with a low percentage and gradually increasing it, but the administration was not always continuous, the inhaler being sometimes removed to examine the corneal reflex or for other purposes. In the course of the pursuance of this method, the percentages being noted throughout, the same form of death was seen, thus affording definite and final proof that the percentage was within the so-called limit of safety, viz., 2%.

At first there was no suspicion of ventricular fibrillation as a cause of death in these cases; when this was suspected later, evidence of it was sought for by opening up the chest and pericardium. When this was performed immediately after syncope the evidence was unmistakeable, but on the other hand if the *post-mortem* was delayed for purposes of attempting the recovery of the animal, then the evidence might be presumptive evidence only, for actual fibrillar contractions might have passed away, but even under such circumstances the absolute inactivity of the ventricles is a suggestive feature. The determining causes of death were not at first apparent, but it became progressively evident that an entire withdrawal or great reduction of the chloroform was a factor of outstanding importance

in the procedure, and such a factor is specifically noted in nearly all my notes of the cases. I am now able to classify the procedures which may lead to syncope under three headings :—

1. On intermitting the administration. On taking off the chloroform the animal dies spontaneously, with or without signs of recovery (*i.e.*, movement, &c.) from the anæsthetic.

2. On struggling. After stopping the administration, or when under a low percentage, the animal was caused to struggle, frequently as a result of tying it down on the experimental table. This struggling precipitated spontaneous syncope.

3. On increasing the chloroform suddenly or on re-applying it after an intermission. On the animal showing signs of recovery either by struggling or by minor evidences, more chloroform was given, and this re-application was quickly followed by syncope.

A complete account of the cases of syncope upon which the above conclusions are founded is given below in chronological order. The descriptions are given just as they were noted at the time. Unfortunately these notes are not in every case very complete, being, many of them, made at a time when the significance of all the circumstances was not fully appreciated.

List of cases of syncope during the induction of chloroform anæsthesia.

CASES.	CAUSE OF SYNCOPE.
1. May the 22nd, 1908. Drop method. Cat came round a little and moved about before tying down on board. Some extra chloroform given when tied down. Gave several strong gasps and found to be dead. No recovery by artificial respiration or on prolonged perflation. No P.M.	Intermission and re-application.
2. May the 29th, 1908. Drop method. Took some time to go under. Made quite flaccid and quiescent and tied down to board, chloroform kept up as before. When tied down struggled pretty violently, about 10 drops quickly applied to the nose bag. Almost immediately after found not breathing and heart not beating. A few gasps, but no sign of heart action afterwards in spite of artificial respiration. No P.M.	Struggling and re-application.
3. September the 12th, 1908. Drop method. When tied down on board struggled and phonated, five drops put on nose bag, within a few seconds the breathing and pulse stopped . . . . . Breathing and pulse gradually recovered. Recovery.	Struggling and re-application.

CASES.	CAUSE OF SYNCOPE.
4. September the 28th, 1908. Drop method. One out of eight cats in which an attempt was made to reproduce this form of death. Struggled very strongly during induction. When it had not had more than three drops at a time it commenced to inflate its chest deeply and respire powerfully apparently against a partly closed glottis, the cat being held by the legs at the time. The heart beat was not readily perceptible, as the chest wall was very tense. Five drops then put on nose bag, breathing quieted down, heart beat still not readily felt, when tail spasm was noted and breathing suddenly ceased. Attempted recovery by chest compression and tongue traction. Cat gave about six gasps at intervals, but the heart never recovered and normal breathing never reassumed. No P.M.	Probably V.F. from struggling, followed by recovery, with re-lapse on re-application.
5. December the 1st, 1908. Drop method. Three to five drops rather rapidly repeated. Went slack early when the heart noticed to be beating very faintly, respiration good. Chloroform discontinued, and the animal tied down when it very quickly came round with a quite strong and slow heart beat. As far as can be remembered two doses of five drops each were then applied. Heart beats soon noticed to be imperceptible, respirations remaining regular and fairly vigorous. Chloroform removed, but breathing gradually failed and animal restored with great difficulty by chest compression and tongue traction. Many gasping respirations occurred before the heart commenced to beat again. Recovery.	Intermission and re-application.
6. May the 17th, 1909. Drop method. Chloroform applied carelessly in large amounts, heart felt to be faint early in administration. Chloroform removed. The corneal reflex was very active and animal moving when it became convulsed strongly on applying a fresh dose, and then heart beat was found absent and breathing ceased. Breathing was restored actively but not the heart. No P.M.	Intermission and re-application.
7. August the 15th, 1910. Drop method followed by *ad plenum.* Put under thoroughly by drop method with the intention of continuing by *ad plenum* method. The apparatus was found not to be working properly, so decided to abandon experiment and nose bag removed. The apparatus was quickly mended however, and experiment resumed, animal now coming round and moving slightly. Given 2% *ad plenum* and proceeded to tie down. When tied down animal found dead and could not recover it. Judging by the want of resistance on tying down the cat expired almost immediately on giving 2%. P.M. Heart exposed. Auricles beating, ventricles not beating. Right ventricle fibrillating very finely at one spot near apex, later fibrillation became more evident generally.	Intermission and re-application.
8. September the 14th, 1910. Drop method followed by *ad plenum.* Chloroform rather pushed, went under readily. Became quite slack and breathing became weak, heart slow but quite palpable, corneal reflex still active. Nose bag taken off and then continued with 2% *ad plenum* method. Soon commenced to struggle and breathe deeply and within thirty seconds became motionless, no heart beat felt, breathing stopped. A few breaths induced by tongue traction, but heart never beat again. No P.M.	Intermission, re-application and struggling.

CASES.	CAUSE OF SYNCOPE.
9. November the 9th, 1910. *Ad plenum* method. Put under by *ad plenum* method gradually increasing vapour up to 2%, then back to 1·5%. Incision made in neck, struggled, put chloroform up to 1·8%, incision continued, struggled again and the funnel slipped off the head. Left under chloroform again whilst attention diverted, then noted breathing stopped and heart not going. Breathing recommenced spasmodically for a short time, but heart never recovered. P.M. Heart distended. Auricles beating rapidly. Right ventricle fibrillating slightly. Left ventricle faint fibrillation later.	Struggling, intermission and re-application.
10. December the 3rd, 1910. *Ad plenum* method. Induction first with 1%, then with 2%. When fully relaxed tied down. Breathing noticed rapid but very shallow, heart beating rapidly but strongly. Percentage reduced to 1·8% when animal suddenly went into a general spasm, commencing in the tail, fully inflated chest which became very tense. Spasm lasted a few seconds and at the end of it the heart found not beating. All efforts at recovery unavailing. No. P.M.	Intermission (not noted but almost certain) and re-application.
11. December the 6th, 1910. Drop method. Cat sneezed and blew the bag off its muzzle when half way under. Bag re-applied, struggled a little, then two or three drops put on and heart found to have stopped almost immediately afterwards. Natural breathing recurred spasmodically, but heart beat never returned. Vagi were cut without result. P.M. Chest opened late. Ventricles quite inactive, did not show any signs of fibrillation ; auricles only beating feebly.	Intermission and re-application.
12. December the 13th, 1910. Drop method. Gradual induction. Heart beat rapid but not strong. Sneezed violently, chloroform continued during sneezing, not in excess. Cat then gave several expiratory groans, chest strongly inflated several times and then collapsed dead. Vagi cut and other methods of restoration tried without avail. P.M. Chest opened late. Ventricles quite inactive and not fibrillating. Heart not over-distended. Auricles beating extremely feebly and at long intervals.	Sneezing and re-application.
13. December the 13th, 1910. Drop method followed by *ad plenum*. Chloroform given fairly rapidly. When apparently well under took off nose bag. Cat sneezed a little and 2% given through funnel. Sudden collapse followed, no recovery. No P.M.	Intermission and re-application.
14. February the 24th, 1911. *Ad plenum* method. 2% from beginning. Rapid heart beat. Quiet for first two minutes of induction, then commenced to sneeze, inhaler removed for about thirty seconds, corneal reflex active. Inhaler re-applied when sneezing had ceased. Amplitude of thoracic respirations almost immediately increased, inflated chest with expiratory groans, heart could not be palpated on account of the tense chest walls. When respiration ceased, as it did quickly, heart beat could not be felt. At the moment of re-application the inhaler was yielding exactly 1·9% vapour. P.M. Chest opened at once. Ventricles fibrillating. Right auricle fibrillating very evidently, left auricle beating rapidly.	Intermission and re-application.

CASES.	CAUSE OF SYNCOPE.
15. March the 2nd, 1911. Induction *ad plenum*, 2% from the beginning.	
Incision in neck made when under, and reduced chloroform to 1·5%. Commenced to struggle violently and chloroform raised to 2%, but previous to this the respirations were increased in a typical manner, with rigidity, so that the heart could not be palpated. No doubt the heart stoppage occurred before the chloroform was increased. P.M. Chest opened some time after. Ventricles fibrillating finely, fibrillation increased by massage. Auricles beating.	Struggling.
16. Date ? Drop method.	
Came round on tying down. A few more drops induced forced respirations and death. No P.M.	Re-application.
17. August the 2nd, 1912. *Ad plenum* method.	
2% chloroform *ad plenum*, for three minutes, breathing quite quietly, not deeply under at any time, heart beating quietly, not fast, corneal reflex present not very active. At the end of three minutes chloroform removed as an intentional test, respiration increased in force almost at once, no struggling, phonated, and breathed deeply. No heart beat felt when spasm of chest had passed off. P.M. Ventricles fibrillating ; right auricle fibrillating faintly, left auricle beating faintly. Right auricle purple, left auricle bright red.	Intermission.
18. August the 2nd, 1912. *Ad plenum* method.	
2% given for about two minutes. The delivery tube to the funnel then became kinked, causing an intermission of the vapour. Phonation, deep breathing and death. No movement or struggling. No P.M.	Intermission.
19. September the 22nd, 1912. *Ad plenum* method.	
(Attempt to kill by chloroform in a series of six cats.) Cat 5. Cut male. 2,128 grms. Had plenty of milk and meat up to evening of 21st, but nothing since. 2.46 p.m. 1% on. *Ad plenum*. 2.50 p.m. 1% off. Heart beat fairly if not quite regular at first. Sneezed once and looked round, no other movement. In about twenty seconds the heart beat was felt to cease suddenly, increased respiration immediately followed. No P.M.	Intermission.
Cat 6. Cut male. 2,455 grms. Fed as No. 5. 2.59 p.m. 1% *ad plenum*, on. 3.3 Spasmodic movement and phonation. 3.3½ Struggling. Chloroform off, heart becomes irregular. 3.4½. 1% on. 3.6½ Struggles strongly. Heart suddenly ceased beating, respiratory spasm and loud phonation ensuing. 3% put on with later gasps, when heart recovered permanently. Recovery.	Struggling during light anæsthesia.
20. January the 14th, 1913.	
Cat put deeply under by unmeasured chloroform vapour in a cup. This induced at first violent struggling and an intense persistent tachycardia. When under, cup taken away, and after a brief interval *ad plenum* method with 2% vapour substituted. Death almost immediately with usual symptoms. No P.M.	Intermission and re-application.

The foregoing account of twenty-one deaths, occurring during the induction of chloroform anæsthesia in cats, sheds an entirely new light upon the conditions of dosage under which they die in this stage of the administration of chloroform. In those cases in which the chloroform vapour was supplied in measured concentrations the factor of overdosage can be excluded with certainty; in many of those cases in which the chloroform was not mechanically regulated, it was administered in such restricted quantities as to exclude the factor of overdose with practical certainty. The condition of the animals in relation to their low dosage may be further judged by the fact that some of them were moving slightly or struggling, and some were in fact in a state of semi-consciousness at the moment preceding the final collapse. Finally when the cats died as a result of the re-application of the vapour the short space of time which elapsed between the re-application and the syncope, the frequently instantaneous sequence, entirely precludes all possibility of a sufficient intake of chloroform to oversaturate the tissues.

When an animal is overdosed with chloroform the respiratory and cardiac phenomena are entirely different from those described above. The respirations gradually become weaker and then fail; they do not become exaggerated or fail suddenly. The heart beat persists after the failure of respiration, and even if not palpable, at least the ventricles may be seen, on inspection of the heart, to exhibit a feeble, but rhythmical, beat for some minutes after respiratory failure; both auricles are seen to be purple in colour as a result of their both containing venous blood; the *post-mortem* appearance of the overdosed heart is thus sufficiently distinctive. After respiratory failure such as that caused by an excessive administration of chloroform, the animal can be resuscitated readily enough by ordinary means; in support of this assertion I may cite the authority of Snow[27] and Paul Bert,[1] who employed vapours up to 6% strength, and this view is, I think, generally accepted. In the majority of my cases the heart did not recover spontaneously, nor could it be restored by any of the methods usually employed for the purpose of resuscitation.

My cats therefore did not die from overdosage; this is demonstrated by—

1. the restriction of vapour;
2. the evidences of light anæsthesia;
3. the mode of respiratory and cardiac syncope;
4. their insusceptibility to resuscitation;
5. the *post-mortem* appearance of the heart.

Any one of these reasons is in itself convincing; taken in conjunction they constitute overwhelming evidence of the truth of my conclusion.*

The symptoms accompanying the syncope were in all these cases compatible with primary cardiac failure from ventricular fibrillation, a

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* In two cases (Nos. 11 and 12) the vagi were cut after death without result. The syncope was therefore not due to Embley's form of vagal cardiac inhibition.

condition which I have shown to be fostered by *light* chloroform anæsthesia, and a condition which was demonstrated in certain instances after death.

As the result of the foregoing observations and considerations I adopted a certain definite plan of administration—I induced anæsthesia more rapidly by giving the animal a fairly full percentage of vapour, 2% or more, to inhale from the commencement. The administration was made a perfectly *continuous* one, never on any account intermitted, and the strength of the vapour never reduced ; if the animal struggled it was firmly restrained, and the struggles were not allowed to interrupt the administration. I have now had an experience of some 300 cases of chloroform anæsthesia induced by this method, with a single instance of death (No. 18), and this death followed the accidental interruption of the administration through a rubber supply tube becoming temporarily obstructed. This experience lends further confirmation to my views regarding the cause of death, for it is in striking contrast to that appertaining to the usual intermitted method of administration in common use, and which has led to the disuse of chloroform as an anæsthetic in many physiological laboratories. Briefly related, it may be said that anæsthesia may be induced with perfect safety with chloroform, provided it is given *of a full strength* and *in a perfectly continuous manner*.

The occurrence of a death as a simple sequence to removing chloroform occurred in only three of the related twenty-one cases of death, but this occurrence is more frequently met with after the conclusion of an operation under aseptic conditions, such, for instance, as excision of the stellate ganglia, performed with the object of allowing the cat to survive ; this fatal conclusion is indeed so frequent that I never now use chloroform for these aseptic operations. This death on recovery seems to be more favourably conditioned by a somewhat prolonged preliminary subjection of the heart to the action of chloroform at a moderate percentage strength ; deep and prolonged narcosis tends to abolish the risk. The syncope may occur within a few minutes of the termination of the operation, or it may be delayed for an hour or more ; it may occur in a perfectly quiescent animal, but is more usually preceded by some form of unconscious movement or by a fit of general excitement. The symptoms of this death on recovery are precisely similar to those described as occurring on intermission of the vapour during induction, and the cause of death is made apparent by laying open the chest and inspecting the heart.

Illustrative case. (August the 2nd, 1911.) Cat. Induction with 2% chloroform, *ad plenum* method. When under, the chloroform was reduced to 1·5% whilst the neck was being shaved. The chloroform was then taken off and a bandage rolled round the neck, and then the animal was laid on its side on a bench to recover. A few minutes later the cat commenced the " running " movements which are so frequently a sign of returning consciousness. These movements ceased suddenly within a few seconds of their appearance, powerful expiratory efforts made their appearance accompanied by loud phonation, and on cessation of respiration no sign of heart beat could be found.

P.M. Chest opened rapidly. Ventricles fibrillating, auricles beating, right auricle purple, left auricle bright red

(b)   Observations made with recording apparatus.

I have succeeded in obtaining graphic records of nearly all the forms of sudden syncope which have just been described as occurring during the induction and recovery stages, and as will be seen, they all conform to the same type, i.e., a sudden collapse of the circulation, invariably preceded by a typical irregular tachycardia.

I have made many and persevering attempts to obtain graphic records of these forms of sudden death occurring in the course of the process of the induction of anæsthesia, but, with some important exceptions, the experiments did not prove very fruitful of results.   Even in intact animals there is no exact procedure which will *insure* the onset of syncope at this stage ;   a number of trial experiments must be performed before attaining a single positive result.   At times a succession of successful reactions have been obtained, but I have never been able to fathom the particular circumstances attending the success of the experiments, and that in spite of modifying the general conditions of the animals in regard to feeding, &c., in many ways ;   a distinct impression is left that the tendency to ventricular fibrillation is one of seasonal incidence.   Under experimental conditions with vascular and respiratory recording apparatus the difficulties of this form of research are multipled.   In one series of experiments I adopted the method of Brooks, by this means following the process of induction from the very commencement, but under these conditions the heart appears to be somewhat less liable to pass into an irregular condition than usual.   The preceding operation no doubt tends to depress the heart and exhaust the suprarenals, for the results are different in degree from those observed in normal intact, and hence vigorous, animals.

A second series of animals was submitted to a preliminary anæsthetisation by pithing the cerebral hemisphere ;   but this method has likewise proved unsatisfactory, for the heart appears to be depressed under such circumstances and, as has already been remarked, the ventricles fail to fibrillate even when directly stimulated by the injection of adrenalin.

The effect of struggling.   In one experiment with Brooks' method I obtained a very significant tracing.   As a general rule in this method the stage of muscular excitement, which is so frequently observed in normal cats, is suppressed, but in this single animal I did manage to induce an excitement stage accompanied by struggling.   The heart thenceforth assumed an irregular tachycardial condition which very quickly passed into fibrillation of the ventricles, and a precipitate fall of blood-pressure from a height of 180 mm. took place.   This experiment is illustrated and fully described in Fig. 19.   There was no excessive intake of chloroform in this experiment, even if such be a possible event at 1% concentration ; further, the chloroform was stopped before death, and this fact may have even accelerated the syncope.   The large fluctuations seen in the respiratory curve are not wholly due to deep breathing, but in part to a mechanical disturbance of the recording

bag through muscular movements, and in fact the animal must have been holding its breath to a certain extent whilst struggling, for the colour of the left auricle was darker than is usual in death from ventricular fibrillation.

With the exception of the exposed artery this animal was otherwise intact, and the experiment may be taken as typical of what happens in death from struggling in the early stages of anæsthesia, which is thus proved to conform to the usual type of death from ventricular fibrillation under light anæsthesia illustrated in previous sections of this paper. I have on many occasions likewise observed struggling cause an already irregular heart to fibrillate in the course of the later stages of an experiment, but these were generally fortuitous occurrences and were unrecorded. Struggling is most deadly after entire removal of the chloroform or after it has been reduced to a very low percentage.

As regards the mode of action of struggling I think there can be little doubt. For some time the relation of a rise of blood-pressure (the mechanical effect of powerful movement) interested me, but although in unanæsthetised animals movement gives rise to considerable alterations in blood-pressure, in the chloroformed animal this effect is largely negligible. I think it can hardly be doubted that the onset of irregularities is the outcome of a state of general excitement, affecting the sympathetic as well as the somatic nerve paths. The subjective evidence of cardiac acceleration in emotional states is a commonplace observance ; apart from this it has been shown by Cannon and de la Paz,[3] and later confirmed by Elliott,[4] that emotional states, such as fright or anger, are accompanied by an increased secretion of adrenalin. In this way in all probability the usual double effect, accelerator and suprarenal, is brought to bear on the heart—just as it is in the case of ventricular fibrillation following a sensory stimulation. Ventricular fibrillation may also be produced under chloroform through the action of strychnine, or by pithing the spinal cord, and in fact I conclude that any convulsive nervous output, such as that which may be said to accompany struggling, may result in a cardiac syncope from ventricular fibrillation.

It is thus seen how the excitement phase of the induction period is a very dangerous one. Violent movements are liable to be accompanied by the onset of cardiac irregularities which may quickly pass into fibrillation or may constitute the precursors of fibrillation from other causes. The onset of these irregularities from struggling may be confirmed with the utmost readiness in the intact animal by such simple means as placing a finger over the apex beat, or by the use of a stethoscope.

The effect of removing or decreasing the chloroform. In Fig. 20 is shown the result of taking off the chloroform, in this case of 1% concentration, in the course of the earlier stages of anæsthesia. There is a prompt increase in the efficiency of the heart's action, resulting in a rise of pressure, and a subsequent transition into an irregular tachycardia of brief duration. I have had many opportunities of observing a similar

reaction at later stages of anæsthetisation ; the heart does not then react so promptly, but I have observed on several occasions ventricular fibrillation to occur as a purely spontaneous sequence to a ventricular tachycardia induced in this manner.
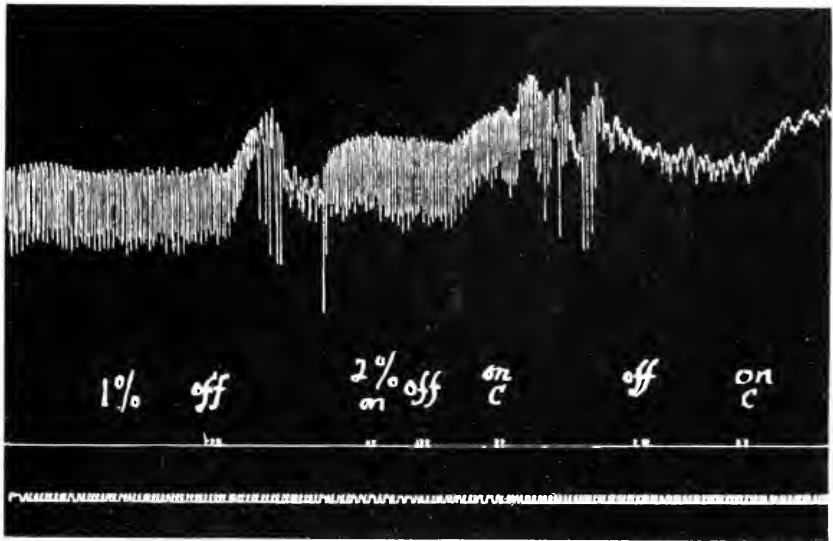

Fig. 20. Blood-pressure curve during the later stages of the induction of anæsthesia (Brooks' method). Cannula in crural artery.
  The heart is stimulated by taking off 1% vapour and passes into a phase of irregularity. The heart fails to respond on re-applying a 2% vapour. On taking off 2% the heart responds once more by a rise of blood-pressure. A glass tumbler containing a piece of wool saturated with chloroform was then put over the animal's head (" on C "), causing the onset of an irregular tachycardia. A later re-application of concentrated chloroform is seen to cause a rise of blood-pressure. The signal line represents the 50 mm. pressure level. Ludwig manometer. Time in seconds.
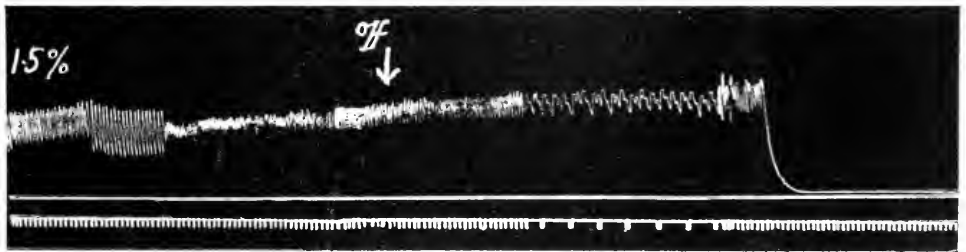

Fig. 21. Ventricular fibrillation resulting from partial recovery from chloroform anæsthesia. At the beginning of the tracing the kymograph was stationary, 2·2% being administered ; the chloroform was reduced to 1·5% and the drum started. The arrow marks the moment of entirely removing the chloroform. At one point the drum is accelerated to demonstrate the cardiac irregularities. For further details see text. Hürtle manometer. Time in seconds. Just before the arrow mark the tracing is slightly blurred owing to a fault in the tracing paper.

Fig. 21 illustrates one out of several tracings I have obtained of this event.
  This cat had been under a 2·2% vapour at the commencement of the tracing. The result of reducing the vapour to 1·5% was an increase in

cardiac action and a rise of pressure from 72 to 88 mm., the rate of beat being 120 per minute. This rhythm suddenly changed to a bigeminal beat, and this again passed into an irregular tachycardia. Forty seconds later the chloroform was removed entirely ; the blood-pressure continued to rise, and after a period of intense tachycardia (about 360 beats per minute) the ventricles fibrillated. This occurred about 45 seconds after removing the chloroform, the ultimate height of blood-pressure being 102 mm.. The animal was perfectly quiescent throughout the experiment, and at its termination it could not be said to have more than partially recovered, as is evidenced by the comparatively low level of the blood-pressure just before fibrillation occurred.

In this and in several similar tracings I have obtained a complete graphic representation of such events as have been described in previous pages as the result of taking off the chloroform, and the process is demonstrated to be exactly similar to that resulting from the action of adrenalin or that of sensory stimulation in that an initial stage of cardiac irregularities precedes the fibrillation.

In Fig. 8 the effect of taking off the chloroform has been illustrated under other circumstances ; the irregular tachycardia was initiated by an irritation of a sensory nerve, but this alone would not have served to throw the ventricles into fibrillation under the existing concentration of chloroform, viz., 1·5%, it was only on taking the chloroform away altogether that this came about. In this way irregularities initiated by struggling, or in other ways during the induction period may terminate in ventricular fibrillation if the administration be subsequently intermitted.

Similarly I have seen on one occasion ventricular fibrillation occur on ceasing the administration of a high percentage of vapour on account of signs of an impending overdosage, the breathing having become nearly, but not quite, suppressed. The blood-pressure then rose rapidly, the heart became irregular, and the ventricles fibrillated at a blood-pressure of 122 mm.. It is easy to understand how, but for the fortunate accident of a tracing, such a fatal result might have been attributed to cardiac depression alone from excessive chloroform.

It is an open question whether in the earlier stages of anæsthetisation another factor may not assist in bringing about a fatal result : this is the stimulation of the nasal mucous membranes by a change from chloroform vapour to pure air. This is not a mere fanciful suggestion, for undoubtedly this change of atmosphere does stimulate the nasal mucosa, as is evidenced by the severe fits of sneezing which frequently follow immediately upon removal of the chloroform. The onset of fibrillation is sometimes so rapid that it does seem at least *possible* that a reflex factor such as this may be involved.

The onset of spontaneous irregularities on a transition to a lighter degree of anæsthesia is a conspicuous event at all stages in the course of experiments under chloroform. If the transition be a gradual one, as may be

the case when the heart has been under the influence of chloroform for some time, the irregularities may appear in a graded sequence from single extrasystoles up to the more complicated tachycardias, a sequence which is in conformity with the view that these different forms of irregularities are expressions of progressive grades of the same pathological process (*vide* Levy and Lewis[21]). In Fig. 22 is illustrated such a slow transition arising from the substitution of a 0·5% vapour for a 2·7% vapour. As the animal passes into a lighter degree of anæsthesia the blood-pressure rises and the heart accelerates slightly so long as it remains regular, starting at a rate of 144 beats per minute and finishing at a rate of 156 per minute just previous to the onset of the first extrasystole, the blood-pressure having in the meantime risen from 88 mm. to 118 mm.. Following this the heart again becomes regular for a few seconds and then breaks into a sequence of trigeminal beats, followed by a series of mixed bigeminal and trigeminal beats. Finally a rapid indecipherable tachycardia ensues, broken at irregular intervals by long pauses.*

The most intense irregularities in such cases appear in the lighter degrees of anæsthesia, the intermediate forms in the intermediate degrees of anæsthesia. It is not my view, however, that chloroform in a particular degree of concentration can of itself initiate a specific form of irregularity, but the onset of irregularities is, I believe, conditioned by the *change of cardiac state* involved in the progress from deep to light anæsthesia ; as the change progresses the irregularities become more marked. Chloroform serves to render the ventricles *irritable*, *i.e.*, liable to exhibit beats of heterogenetic and ectopic origin, but these only occur when it is subjected to some further form of *exciting* cause, such as a cardiac stimulation. The heart may be maintained beating at a perfectly regular rate even when lightly anæsthetised so long as the anæsthesia is a level and unchanging one, and no other disturbing influence is at work, such as arise from sensory stimulations. This is best seen in the intact animal. If a cat be anæsthetised gradually with chloroform and kept quiet and undisturbed the whole time, the heart continues to beat regularly even when the anæsthesia is light. Thus in one instance a cat was anæsthetised with a 1% vapour, it was petted and stroked, and remained perfectly quiescent until it became unconscious. The same vapour was administered continuously for thirty minutes, and the heart remained perfectly regular the whole time.† If, however, in a cat so anæsthetised, the chloroform be entirely removed, the heart is liable to become irregular, and the ventricles may eventually fibrillate. Similarly, irregularities may appear, not on total withdrawal, but on a change to a lighter degree of anæsthesia alone, and I have little doubt that the exciting cause of the ectopic beats is identified in the change of cardiac state involved in its release from the

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* Indicated by the drops in the curve.

† A like result was obtained on administering 0·7% chloroform for over an hour. A few extrasystoles were in this case noted during a short period of violent retching.

depressing action of the chloroform, this release being, in effect, the equivalent
of a cardiac stimulation, just as release from the depression of vagal control
is the equivalent of a cardiac stimulation.
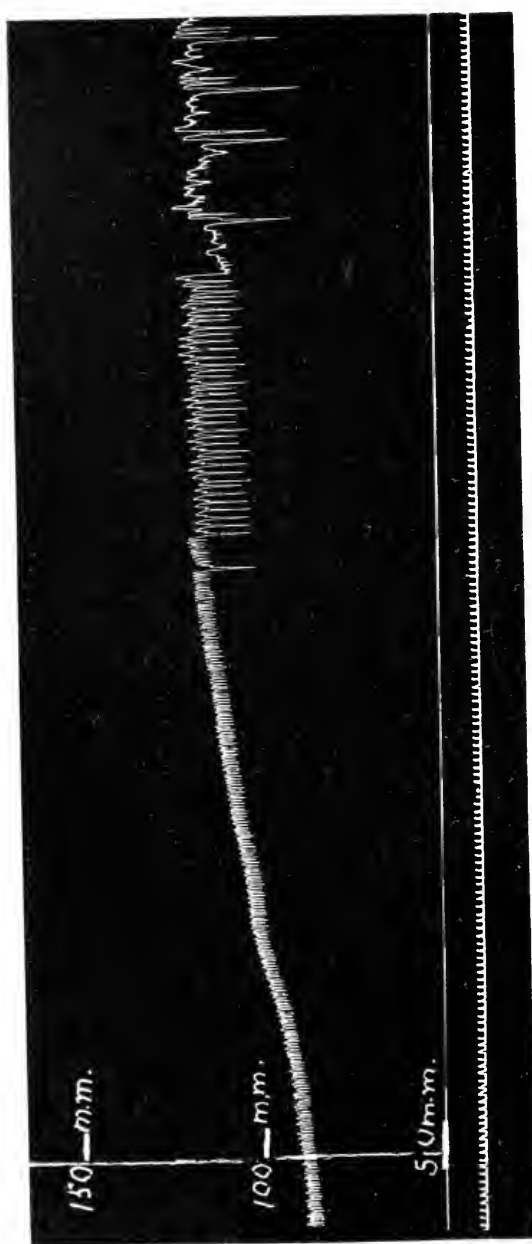
Fig. 22. A rise of blood pressure followed by progressive stages of irregularities resulting from the passage from a deep to a light anæsthesia ; for detailed description see text. Ludwig manometer. Vertical scale indicates blood-pressure. Time in seconds.

The depression of cardiac function by chloroform is an accepted fact,
and I need give but a single reference in this connection, viz., the work of
Sherrington and Sowton[26] upon the isolated mammalian heart. These

experiments demonstrate a progressive depression of the force of ventricular contraction down to extinction on perfusion with solutions of chloroform of progressive strengths, the rate of heart beat remaining unaltered ; on washing out the chloroform from the heart this regains its full force of action once more.

In the intact animal a similar effect is noted ; on removing the chloroform the blood-pressure rises, mainly through the increased efficiency of the heart beat ; there is also, however, in this case, distinct evidence of acceleration on recovery, but this is never, so far as I have observed, a very marked acceleration, comparable, for instance, with that resulting from section of the vagi (I am speaking, of course, of rhythmic acceleration only, and not accelerations due to heterogenetic beats). In the instance already cited (Fig. 22) the acceleration was 144-156 with a pressure rise of 30 mm. ; in another instance the change of rate was 127-150 with a pressure rise of 35 mm. ; in yet another case the change of rate was 108-144 with a pressure rise of 26 mm.. It must be admitted therefore that this form of stimulation is possibly somewhat different from that occurring on section of the vagi, and it appears probable that the stimulation arising from recovery of depression caused by chloroform affects the heart mainly in respect of one of its functions, viz., its force of action. This particular function is predominantly affected by the action of adrenalin, it is affected equally with acceleration as a result of nervous stimulation or of vagal section, and it is thus uniformly affected in all my experiments ; it is, however, impossible to allocate at present to any one function of the heart a chief part in the mechanism of the production of ventricular irregularities ; all the functions so far as is yet known may play a part.

These considerations afford an indication of the manner in which high percentages of chloroform vapour serve as a protection from the incidence of ectopic beats and ventricular fibrillation. Apart from its depression of the reflex nerve centres, deep narcosis tends to depress and dilate the ventricles, and thus by a direct cardiac action counteracts the effects of stimulation, either totally, so that the heart remains regular, or in part, so that although abnormal beats may be excited, yet the stimulation cannot produce its most profound effect, viz., ventricular fibrillation.

Interesting support to the above observations and considerations is afforded in some casual observations by Sherrington and Sowton[26] in their experiments already referred to. In a table of results (British Medical Journal, July the 23rd, 1904, p. 168), it is noted that on washing out a strong chloroform solution from the perfused heart and thus allowing it to recover, it was liable to pass through a stage of fibrillar contractions. I gather that this was observed in the *recovery* stage only, and never during continuous administration with any concentrations of chloroform in the perfusion fluid. These observations are likewise interesting as tending to confirm my suggestion that the ventricular fibrillation arising from stimulation of the heart under chloroform is an intracardiac and not a nervous phenomenon.

The re-application of chloroform. It has been seen how reduction of the anæsthetic may initiate cardiac irregularities, which may terminate spontaneously in fibrillation, or may terminate in fibrillation as a result of the added stimulus of struggling or of re-application of the vapour. This latter procedure has now to be considered. When first noted, I was unable to decide whether death was a *post hoc* or *propter hoc* effect of re-application, but the great frequency with which the two events have been associated leaves no room for doubt that the one is the exciting cause of the other.

I have already cited several cases of death from this cause which prove that it may be brought about by chloroform vapour of ordinary anæsthetic strength, *i.e.*, at or under 2%, but it does appear to be more readily conditioned by a vapour of higher concentration, and by using such stronger vapours graphic records have been obtained on several occasions. In Fig. 20 the effect of re-application in the earlier stages of administration is shown ; 2% is ineffective, but a concentrated vapour causes the heart to pass into an irregular tachycardia. I have on several occasions been enabled to obtain tracings showing ventricular fibrillation as a result of re-applying a concentrated
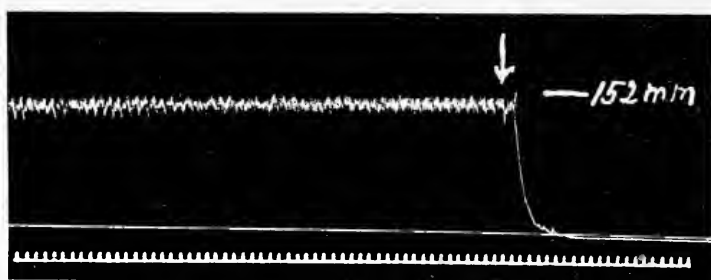

Fig. 23. Ventricular fibrillation resulting from the sudden administration of a concentrated vapour to a cat which had not been inhaling any chloroform for two minutes, the heart exhibiting a rapid irregular tachycardia. The animal was perfectly quiescent but the application caused a slight general reflex spasm, and was almost immediately followed by V.F. The arrow marks the moment of re-application. Hürtle manometer. Time in seconds.

vapour to an animal not under any anæsthetic at the moment, and in which the heart was already in a state of tachycardia ; Fig. 23 shows this reaction very well. In this case the reaction was almost instantaneous, as it generally is, but it may be delayed as much as 30 seconds from the moment of re-application. It is conclusively shown in this tracing that the cardiac syncope was not the result of an " overdose " in the ordinary sense of the word, although the vapour was certainly very strong, being exhibited by putting absorbent wool containing a considerable quantity of chloroform into a glass tumbler, and putting this over the head of the cat. There was, however, not sufficient time before syncope occurred, for the vapour to produce any depressing effect, as is evidenced by the fact that the blood-pressure at its final elevation was 152 mm.. The cat was, in fact, still lightly anæsthetised when it died.

When a strong irritating vapour is given suddenly to a lightly anæsthetised cat it may, and often does, cause the animal to struggle, and this struggling alone may then of course account for fibrillation. When struggling does not occur, a slight general muscular twitch is frequently observed at the moment of re-application; the animal appears to become slightly tense, as was the case in the experiment from which Fig. 23 was taken, and this fact points to the probability that the onset of fibrillation is conditioned largely by a reflex sensory stimulation, just as an irritant vapour like ammonia produces a reflex cardiac effect.

Apart from the above considerations it appears probable that the first effect of chloroform upon the heart is a stimulating one, and there is in fact direct evidence of this in the experiments of Sherrington and Sowton[26] already alluded to; the effect is not a very marked one, but it is perfectly evident and is remarked upon by the authors. In this respect chloroform shares with most other anæsthetics the property of being a stimulant in the initial stages of its action.

It is, therefore, highly probable that the effect of re-subjecting the heart to chloroform, after having allowed the former effects of the anæsthetic to partially wear off, is a further stimulation of the ventricles through both reflex and direct means, and in this way constitutes a further exciting cause of ventricular fibrillation.

The fact that the re-application effect is more readily observed when the vapour is strong constitutes, so far as I have observed, the only particular instance in which a strong vapour more readily conduces to ventricular fibrillation than a weak one, and this greater facility of causing syncope with a stronger vapour in this single set of circumstances has, I believe, been mainly responsible for the support which has been accorded to the idea that all deaths under chloroform are the result of overdosage. To this point I shall refer again later.

(c) *The apparently spontaneous deaths in man during the induction and recovery periods of chloroform anæsthesia.*

I have dealt at considerable length with the induction stage of chloroform anæsthesia in animals, because it is one of great practical importance, for a majority of the deaths in the chloroformed human subject occur before the operation has been commenced. It is stated (*vide* Leonard Hill, British Medical Journal, April the 17th, 1897) " that in one year, out of forty-one recorded deaths from chloroform, thirty-nine occurred during the primary stage of anæsthetisation and before the surgeon had touched the patient." In John Snow's book fifty fatalities are recorded, and out of these twenty-eight occurred before the operation was started.

In an appendix to the Report of the Anæsthetic Committee of the British Medical Association (July, 1900) there is a collection of chloroform fatalities which appeared in the press in the year 1892. These deaths number twenty-four, and of them, fourteen occurred during the period of induction of

anæsthesia, and four (Nos. 4, 7, 15 and 18) after completion of the operation and while the patient was recovering. Out of these fourteen induction cases seven were too briefly reported to allow of any analysis (Nos. 1, 9, 10, 11, 17, 20 and 22). In one case (No. 2) death was obviously due to *intermission* as the chloroform container of the Junker inhaler became detached, a fact which was discovered after death. In one case (No. 13) *struggling* followed by*intermission* was the cause of death. In three cases (Nos. 5, 18 and 12) *struggling* alone killed the patient. In one case (No. 23) *struggling* and *re-application*, and in the other (No. 16) a fit, described as epileptic,* immediately preceded death. The remaining cases are referred to later in this paper.

I give here a single instance of a completely reported case taken from Snow's book on Anæsthetics ; it serves as an excellent clinical counterpart to some of the cases of death during induction in cats related in this paper, all the three causal factors of syncope, viz., excitement and struggling, intermission and re-application being particularly well defined. There can be no question but that this man died from ventricular fibrillation.

CASE 17. " The patient, a man, thirty years of age, was affected with hydrocœle. The chloroform was poured on a little cotton, which was placed at the small end of a cone, into which the folded towel made use of was rolled. About a drachm and a half was first poured on the cotton, and the patient was told to inhale in long and deep inspirations. This quantity being nearly evaporated in two or three minutes, a drachm more was added. After a few inspirations rigidity and struggling came on ; these subsided, but in a little time returned more strongly than before, and the towel was removed from the face until the struggling ceased. The patient, however, not being sufficiently insensible to undergo the operation with the necessary quietness, the towel was re-applied, when, after a few inspirations, the pulse suddenly ceased. The face and the whole surface of the body turned pale, the eyes rolled upwards and inwards, and the breathing became very slow, but full and deep, the intervals between the inspirations becoming longer, until the respiration ceased altogether. The patient died before the operation was begun, and within five minutes from the commencement of inhalation. During the application of various means of resuscitation, including the dropping of cold water *guttatim* on the epigastrium, the breathing returned and continued for the space of three or four minutes ; but the pulse and sounds of the heart did not return."

The exact procedure adopted during induction is rarely recorded in reports of chloroform syncope. The method is generally an intermittent one, and is frequently characterised by a *want* of method. The patient may be inhaling chloroform one minute and inhaling none the next, so that the administrator may be unaware of the extent of the intake of vapour, much less be able to report it. I have, however, selected three other cases of death during the induction period for insertion in the Appendix to this paper (Nos. 3, 4 and 5) as they present points of some interest ; in one of them the percentage of vapour inhaled is recorded.

In those cases in which the patient dies during recovery from anæsthesia on completion of an operation, the anæsthetist's attention is usually relaxed, and precise details are in consequence lacking. The following is a typical report of this kind :

Lancet, September the 11th, 1897. " A boy, aged fifteen years, had been anæsthetised with chloroform for the removal of post-nasal adenoids. The operation had been completed and the anæsthetic withdrawn, when the patient was noticed to be breathing deeply. The operator observed some peculiarity about the colour of the face, but was reassured by the presence of free respiration. The respirations, however, suddenly ceased, and all efforts to resuscitate the patient failed."

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* A so-called epileptic fit is not infrequently alluded to in reports of chloroform fatalities. It probably corresponds to the terminal asphyxial convulsions noted in my experiments.

DISCUSSION.

The facts given in this paper throw an entirely new light upon the cause of death under chloroform, and provide data competent to explain every form of death under chloroform which has been described in the human subject. A few typical cases have been described in this paper, but a full clinical discussion of these new facts must be reserved for a paper dealing more particularly with this aspect of the matter.

The large mortality incidence of the induction period in the human subject is fully explained on the basis of my theory of death under chloroform ; the induction stage is *par excellence* the stage of light anæsthesia ; it is moreover the stage of excitement. Very little chloroform has been packed away in the tissues of the body in the earliest stages of administration, and this little is excreted with remarkable rapidity on lessening the alveolar vapour tension of chloroform, and hence the patient " comes round " with great readiness ; this is a fundamental clinical experience. It is remarkable that the prevalence of death in the induction period has never before been associated with this period, regarded as one of *light anæsthesia*.

In the series of twenty-four cases referred to, published in the Appendix to the Anæsthetic Committee's Report, eighteen have already been mentioned as occurring during the induction and recovery stages. In the remaining six the operation had been commenced. One of these (No. 19) was an unexplained case of " respiratory failure " occurring after the patient was put back to bed. In two (Nos. 14 and 26) the death was caused by *re-application* after an interval during which no anæsthetic was given, in the early stages of operation. In one case (No. 24) death occurred *on the first incision*, and in the remaining case (No. 25) the patient died in the early stages of operation, having shown abundant evidences of imperfect anæsthesia.

It is a remarkable fact that in not one of these cases was there any suggestion that an overdose of chloroform had been given, or in fact any evidence to support such a view. This indeed is the common story—the evidences of light anæsthesia entirely outweigh those of deep in nearly every case in which sufficient clinical details are given to enable one to form an opinion.

It is not surprising that the Anæsthetics Committee arrived at certain sweeping conclusions regarding the dangers of incomplete anæsthesia (see pages 122 and 123 in their Report). These conclusions were based on an elaborate analysis of a large number of reports of cases, mainly cases of the administration of chloroform and its mixtures, and they constitute the strongest possible support to my views regarding the source of danger under chloroform ; it is in fact almost incomprehensible that the bearing of this valuable report should not have been better appreciated. This danger of light anæsthesia as opposed to deep is, it is pointed out, associated with the administration of chloroform, and not of ether.

The following important conclusions in regard to chloroform are stated among the final general conclusions in this report :

" XVI. When danger occurs under chloroform, whatever its exact nature may be, there is abundant evidence that in a large proportion of cases the symptoms that are observed are those of primary circulatory failure."

" XVII. Imperfect anæsthesia is the cause of a large number of cases of danger under chloroform."

" XIX. Struggling is very much more frequent in the complicated cases under chloroform than in the uncomplicated, and this phenomenon must therefore be regarded as a source of grave danger under chloroform."

In the face of these findings, it is somewhat surprising to find that the accepted theory of death under chloroform remains that of overdosage, and the accepted theory of safe administration is the limitation of the strength of vapour to the very lowest point of efficiency.

It is impossible within the scope of this paper to deal with the immense amount of controversial literature upon the subject of chloroform syncope, or to follow the work which has led to the adoption of this theory, but the main features are as follows :—

One of the earliest and most scientific workers on chloroform, John Snow,[27] expresses himself as follows (pp. 120-121) :—

" If it were possible for a medical man to mistake or disregard the symptoms of approaching danger, and to go on exhibiting vapour of chloroform, diluted to a proper strength, till the death of the patient, this event would take place slowly and gradually, as in Experiment 23, related above, and every other experiment in which the air did not contain more than five per cent. of vapour. The action of the heart would survive the respiration ; there would be a great tendency to spontaneous recovery, and the patient would be easily restored by artificial respiration, if it were performed whilst the heart was still acting ; *as I have always found it to be successful in animals under these circumstances.*"

The truth of these words is practically admitted by all subsequent observers ; Paul Bert,[1] working with vapours up to 5·4% strength, concluded likewise that the heart always continued to beat after the cessation of the respiration as a result of overdosage. I may add on my own authority[19] that chloroform, when administered to the human subject by ordinary methods, cannot exceed 6% in concentration and can rarely approach that value. There is no evidence to show that higher percentages than 6%, when *continuously* administered till overdosage ensues, will affect the heart in any other fashion, or that recovery is any the less possible when promptly attempted. Observations on the *continuous* administration of vapours of higher than 6% value are wanting so far as I am aware ; but there is no reason to believe that the heart is in such cases affected in any different manner : such observations would be in any case of little practical importance, for these percentages are outside the range of ordinary usage.

How then does the theory of sudden death from overdosage come about ? Snow was well aware that all *fatal* cases of chloroform syncope were due to primary cardiac failure, and the Anæsthetics Committee so recently as 1900 came to a very similar conclusion. Unfortunately Snow was the servant

of his method, viz. : the titration of doses, and he appears to have sacrificed his better judgment in the interests of this method. He apparently searched about until he found a procedure which appeared to prove that very strong vapour, *i.e.*, 8% to 10%, would produce the primary cardiac failure he was looking for. The fallacy underlying Snow's conclusions will be apparent from the following quotations from his book :—

Page 116. "In every instance in which the quantity of vapour in the air breathed by the animals was from three to six per cent., the respiration ceased whilst the sounds of the heart were still very distinct ; in many instances the heart continued to beat from two to three minutes after the breathing had ceased. . . . . . When, on the other hand, the air breathed by the animals contained eight or ten per cent., or upwards, of vapour or chloroform, the action of the heart was always seriously affected and rendered extremely feeble, if it did not actually cease, at the time the breathing was arrested. In several instances, indeed, the sounds of the heart entirely ceased before the breathing, as in Experiment 25, and although the chloroform was withdrawn . . . . . it very rarely had the effect of restoring the heart's action."

The experiment No. 25 referred to above, and upon which Snow relies as one of his chief arguments in favour of the occurrence of sudden and permanent heart failure as the result of overdosage, may be briefly abstracted as follows :—

Page 111. "A cat was placed in a jar containing 4% chloroform vapour. It was removed in a passive state at the end of two and a half minutes. The respirations and heart sounds were quite natural. It was then made to breathe through an inhaler yielding a strong vapour (presumed to be about 10%). After four or five inspirations from the inhaler the heart ceased to beat, the respirations still going on. The inhaler was removed when the heart ceased to beat, and there were two or three rather convulsive respirations afterwards, and then the breathing stopped. The chest was opened ten minutes after death. The heart appeared quite motionless when first observed, but after exposure to air for a short time, there were some slight contractions of a few fibres of the right ventricle."

Overdosage had no direct relation to the fatal result of this experiment, for the procedure was that of *intermission* and *re-application* which I have repeatedly demonstrated to result in fatal syncope with *vapours of ordinary anæsthetic concentration*. It is, for instance, strictly comparable with case No. 14 on page 357 in which the strength of vapour never exceeded 2%.

In the whole of the experiments upon which Snow founded his theory of primary cardiac syncope from the inhalation of strong chloroform vapour (those which he has published are but few in number) similar confusing factors are palpable, that is to say, interrupted administration, struggling and re-application of vapour. In fact there would not appear to be anything in these experiments that cannot be produced by an ordinary anæsthetic strength of vapour. (*Vide* p. 119 in Snow's book.)

Snow's comments upon the fifty collected cases of chloroform fatality are a revelation in perverted interpretation. In many the evidence of primary cardiac syncope, which he acknowledges, is graphically described, but at the same time the evidences of light anæsthesia are remarkably clear ; yet Snow persistently ascribed these deaths to the action of an excessive vapour of over 8%. In some of these cases Snow's own inhaler was employed, which he estimated did not supply more than a 4% vapour,* but this fact did not suffice to satisfy him of his error.

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* Normally this apparatus does not yield more than 3·5% vapour with a medium force of inspiration.

Unfortunately chloroform research has followed on much the same lines ever since ; no doubt the fact that a strong vapour is more effective than a weak one in producing the " re-application " effect has conduced to the survival of this error. MacWilliam[22] fell into exactly the same pitfall. He observed sudden cardiac failure in three instances in cats, and on the evidence of these instances alone he appears to have satisfied himself that primary cardiac syncope may occur as a result of overdosage. These three cases are fully described ; they belong most distinctly to the category of death from intermission and re-application, and are undoubtedly the result of ventricular fibrillation.

There is, with the exception of Embley's work, no other experimental evidence upon which a theory may be formulated of death from primary cardiac syncope under chloroform as a result of overdosage.

Dr. Embley's[5] work on the vagal phenomena of the induction period is too well known to require much comment, but his results are of somewhat doubtful practical significance. The liability of the heart to vagal inhibition was demonstrated in animals which had been very heavily dosed with morphia in addition to chloroform, 0·25 to 0·5 grammes of morphia, and the tendency of morphia to favour vagus effects is well known.

Embley likewise reproduces two tracings which demonstrate, in non-morphinised animals, a similar cardiac inhibition occurring at a blood-pressure level of 25 mm. Hg. or thereabouts, as a terminal event following the administration of concentrated, unmeasured, doses of chloroform, sufficient to depress the heart rapidly. Such experiments have no clinical counterpart, and further there can, I think, be no question at all, on the evidence of Embley's own tracings, that the heart so inhibited is subject to recovery in every case on the prompt application of restorative measures. Embley's experiments never favoured the chances of recovery, although the tendency to recovery was obvious, and it still remains to be shown that this vagal effect of overdosage may be in fact a cause of irrecoverable, *i.e.*, fatal inhibition of the heart.

There remains the prevalent idea that sudden death may result from the *reflex* inhibition of the heart through the vagi, although this of course has no relation to overdosage. This theory I have already discussed at some length on page 347, and I have shown that there is no valid evidence to support it.

I may here briefly refer to two observers who have worked on less conventional lines and have been nearer to arriving at a true conclusion.

The late Dr. Robert Kirk[12], who held strong opinions regarding the relation of light chloroform anæsthesia to sudden death, performed an extensive series of experiments in which he observed, by means of a stethoscope, intense cardiac irregularities resulting from a suspension of the administration of chloroform, and in one case he noted the entire cessation of cardiac action

for 60 seconds; I have derived some valuable indications from his papers. Dr. Kirk refers to MacWilliam's work on ventricular fibrillation and suggests it as a possible explanation of the question. Professor Fraser Harris has kindly sent me some unpublished tracings of experiments performed by him in conjunction with Dr. Kirk in which various irregular tachycardias occurring under light chloroform anæsthesia in a cat may be recognised. Another tracing shows a period of complete heart failure in a dog poisoned with phosphorus and under chloroform. Unfortunately Dr. Kirk did not follow up this line of research further, but formulated a theory which did not find general acceptance.

The other observer is Dr. Alex. Wilson[30] who was led to believe from clinical observations alone that human subjects died from sudden vascular failure under light anæsthesia. From the observation of the occurrence of convulsions and asphyxial respiratory spasm (such as he had seen on the rupture of an aneurysm and in like cases) he deduced a sudden collapse of the circulation, an acute application of physiological principles, but his further suggestion that the event was due to a sudden vasomotor paralysis has not received confirmation.

MacWilliam[22] observed ventricular fibrillation on several occasions in chloroformed animals. He thought that it was conditioned by an excess of vapour. It is natural that he failed to find it, in this connection, a satisfactory explanation of sudden death. He concluded that " it does not appear to be a primary mode of cardiac failure from the inhalation of chloroform in the healthy animal."

This brief review of the work performed upon chloroform syncope tends to show that there is no mechanism with the exception of ventricular fibrillation which can be demonstrated to bring about a rapid and permanent primary cardiac syncope. This is a condition peculiar to light and not to fully established chloroform anæsthesia.

I may add a final word to explain my views in regard to overdosage. Of course animals and men can be killed by the persistent administration of chloroform, and the stronger the vapour the more rapid the death. This has been abundantly demonstrated in animals. It has also been abundantly demonstrated that overdosed animals recover if the ordinary means of resuscitation are promptly applied. So in man; the respiration, and even more rarely the radial pulse, may be suppressed by overdosage, yet recovery is brought about by prompt measures of resuscitation, generally very readily so; it is inconceivable that such measures should be too long delayed even in the hands of the most casual administrator of anæsthetics. I will concede that repeated overdosage may prove fatal, or that overdosage in an asthenic individual may prove fatal, but I do not believe fatal overdosage ever occurs as a result of ordinary anæsthetic methods in those sthenic individuals who form by far the greater proportion of the victims of chloroform anæsthesia.

General Conclusions.

1. The mammalian heart, when under the influence of chloroform, is in an " irritable "* condition. This irritability is raised under conditions of light anæsthesia, and lowered under conditions of deep anæsthesia.

2. Abnormal ventricular beats are evoked in a heart under chloroform by conditions which stimulate it or by equivalent conditions which remove or reduce depressing influences.

3. Under conditions of light chloroform anæsthesia the ventricular irregularities resulting from cardiac stimulation may terminate in ventricular fibrillation and death of the heart.

4. Stimulation of the heart may be effected :—

    (a) As a reflex from sensory excitation ;

    (b) As a result of an intermittent administration of the anæsthetic.

    (c) As a result of the state of nervous excitement accompanied by struggling induced by chloroform in the earlier stages of its administration.

5. Ventricular fibrillation is a cause of death under chloroform, probably the only cause of any moment. It can be prevented by steadily maintaining a full degree of anæsthesia.

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* The term " irritability " of the heart has been generally employed in this paper to denote a tendency to the exhibition of beats of heterogenetic origin.

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Appendix.

Additional reports of clinical cases which illustrate the points dealt with in the body of the paper.

(1) A case illustrating non-fatal cardiac syncope occurring in the course of an operation.

This case occurred in my own experience when I was practising anæsthetics some years ago ; my own form of chloroform inhaler was being employed.

"Female aged 55. Operation for large mammary carcinoma.

Put under chloroform very quietly and gradually, reaching a maximum of 3 per cent.

Incision made at 3 per cent. ; a faint corneal reflex and slight expiratory phonation being evident at the time.

The index was very soon put back to 2 per cent., and maintained there, pupil being small ; colour, and breathing good.

During the stripping of the tumour the pupils became a little bigger, about 2·5 mm. in diameter, and the colour paler, and the vapour was reduced to 1·5 per cent. in consequence ; but as the colour did not improve and the corneal reflex was found absent, the inhalation was then stopped. Shortly after this the pupils were noticed to be very dilated, and the pulse absent, but the breathing remained good and unobstructed.

The patient was placed in the ' feet-up ' position, when the breathing ceased.

Chest compression quickly caused the breathing and pulse to return.

The operation was resumed at 1 per cent., the pulse again became faint during the clearing of the clavicular glands.

Total time of operation : Forty-four minutes, the pulse being excellent at the finish."

(*Proc. roy. Soc. of Medicine*, Vol. II, Part I.)

This patient was very carefully watched from the commencement for symptoms of over-dosage, and there was nothing to suggest that anything was wrong until the tumour was being stripped off the muscles ; on the onset of pallor in accordance with the accepted teaching at this time the chloroform was at once reduced, and subsequently entirely removed, with an almost fatal result. As I would now judge, the pallor and slight dilatation of the pupils were both evidences of a reflex sympathetic action with probably a co-existing ventricular tachycardia, and an indication for keeping up a full degree of anæsthesia ; the result of stopping the inhalation entirely was a progression to ventricular fibrillation which fortunately was of temporary duration only. I reported this case as an instance of how the most careful regulation of the chloroform will not obviate a form of cardiac shock, but I did not at the time appreciate how near this patient came to death.

(2.) This case is taken from the Final Report of the Special Chloroform Committee of the British Medical Association. The regulating inhaler employed was of the Vernon Harcourt type.

" Female aged 31, who suffered from exophthalmic goitre.

The anæsthesia was devoid of any abnormal phenomena, and death, which occurred when the thyroid tumour was being drawn from its attachment, was sudden and of the cardiac type, no doubt arising from ' vagal inhibition.'

The patient was anæsthetic, but not profoundly narcotised at the time of collapse, 0·5 per cent. was being inhaled."

(Supplement to the *British Medical Journal*, July 29th, 1910, p. 63.)

(3.) A case reported by myself some years ago. It illustrates the form of death by intermission and re-application in the induction period. The signs of imperfect anæsthesia were abundantly evident up to the moment of death, and it was this case, observed in January, 1906, which first induced me to seek for some explanation of sudden death apart from that generally accepted, *i.e.*, overdosage.

"Male, aged 47. Weight 15 st., fat and flabby, pasty complexion.

Under treatment for diabetes, 2·2 per cent. of sugar in the urine (total sugar not recorded). Proposed operation, removal of big toe for necrosis ; administration by Dr. Levy's inhaler, complete anæsthesia induced in seven minutes, with a maximum vapour of 1·8 per cent.

A delay now ensued in consequence of the theatre not being ready, and the patient was allowed to come round a little, when he commenced to vomit, and the facepiece had to be removed and cleaned. There was subsequently cause for expedition, and the inhalation was continued at 3 per cent., but as the breathing was restrained and embarrassed by a tendency to retch, he failed to go under.

Suddenly the type of breathing changed, the respirations becoming very deep and forcible ; not more than six or seven of these respirations had been taken when the pupils were found to be widely dilated, the face very pale, and radial pulse imperceptible. Respiration quickly ceased. Fitful attempts at spontaneous respiration were produced by appropriate treatment, but the heart never recovered."

(4.) This case is taken from Snow's book and is a report by Mr. Paget of the death of a boy of nine years occurring at St. Bartholomew's Hospital in 1856. The first page of the report relates to the induction which was irregular and prolonged, and this I have omitted.

" I was on the point of commencing the operation, but as he again, by movements, indicated some degree of sensibility, and changed his posture, about forty drops more of chloroform were poured on cotton wool, inclosed in a fold of lint, an inhaler, with the chloroform on a sponge, having been previously used. The lint was held, about half an inch from the face, by Mr. Thomas Smith, my usual assistant in operations. The patient inhaled lightly for a few times, then made one long inspiration, and appeared to pass at once into deep sleep. Except that he thus appeared to come suddenly under the full influence of chloroform, no external change was visible ; but, a few seconds later, his pulse, which had been carefully watched, and had been to this time normal, suddenly began to beat very quickly ; then it ceased for two or three seconds ; then beat rapidly several times, with a kind of flickering movement ; and then ceased to be perceptible.

Just before this change of the pulse was observed, the chloroform had been withdrawn. The one deep inspiration was followed by a few stertorous breathings, but after these he breathed naturally, his complexion and features showed no change, he seemed only calmly asleep, and in this state he continued breathing naturally, and with no change in his appearance, but pulseless, for at least a minute. Then his breathing became less frequent, and seemed as if it might soon cease ; his face grew pale. and his lips very slightly livid. . . . . .

I refrain, at present, from all comments on this case. Only, I wish to call particular attention to the fact that good breathing was maintained, and, after a suspension, was renewed, long after the heart had ceased to act with sufficient force to produce a pulse at the wrist. And I would add, that this narration is sanctioned and considered to be exact, by the four gentlemen who were to have assisted in the operation, and to whom I am greatly indebted for their counsel and assistance in the greater difficulty that we had to cope with."—*Medical Times and Gazette,* 1856, Vol. i, p. 236.

This abstract is given here mainly on account of the description of the condition of the pulse which preceded death, and which is a vivid word picture of the irregular condition shown in some of my pressure curves.

It is not quite clear from the text whether withdrawal of the chloroform or its re-application immediately preceded death, but both these procedures are mentioned.

" (5). Woman, aged 49. Pale and thin.

Anæsthetic : Chloroform, 2 drachms ; a little ether added towards the end of induction. Induction gradual, by drops on open mask, held all the time about an inch from the face. Some slight irritative coughing at first in spite of very gradual administration. This ceased and there were slight muscular movements of the limbs and a little muttering ; no struggling. Respiration quiet and regular. Lips and ears very good colour. Pupils medium, corneal reflex brisk. Then sudden alteration in breathing (five minutes after beginning of induction). There were seven or eight deep sighing respirations, and at the same moment wide dilatation of the pupil, pulse disappeared, no pallor for ten or fifteen seconds. Then cessation of respiration (no respiratory embarrassment at all before the sudden collapse). Tongue pulled forward, artificial respiration, oxygen, strychnine, &c. No further sign of life.

The symptoms came on a very few seconds after a fairly brisk corneal reflex had been obtained, only a few drops had been added, the mask was always a little off the face."

Judging by the final remarks death would appear to be due to a re-application, " only a few drops," probably (and this can only be surmised) after an intermission ; the description of method is of the usual vague nature. The degree of anæsthesia was carefully noted ; it was of a light description, and the mode of death from sudden primary cardiac failure is evident. There can be no other explanation of this death but that of ventricular fibrillation.—*Proc. roy. Soc. of Medicine,* Vol. 5, No. 2 (Section Anæsthetics.)

THE INNERVATION OF THE ADRENAL GLANDS.
By T. R. ELLIOTT, M.D.[1]

(*From the Research Laboratories of University College
Hospital Medical School.*)

RECENT work has proved beyond doubt that the splanchnic nerves
control the excretion of adrenalin from the adrenal glands, and that the
curve of blood pressure rise caused by their electrical stimulation is the
resultant of two components, namely the direct reaction of the vascular
muscles to the nervous stimulus and the secondary effect on the heart
and blood vessels of the adrenalin thrown into the circulation. This
fact, that the splanchnics contain glandular secretory nerves for the
adrenals, revives a question of great morphological interest. Langley's
analysis of the known glandular nerves, whether they be for the secretion
of sweat or saliva, proved that all conform to the type peculiar to the
autonomic system, a ganglion cell relay being placed on their path
between the spinal cord and the peripheral gland cell. Gland cells
with such innervation naturally belong to the peripheral tissues of
the body.

But the embryological observations of Balfour, and their enlarge-
ment by Kohn and others, have suggested that the chromaffine cells of
the medulla of the gland are derived from the same tissue as that which
gives birth to the sympathetic ganglion cells, and that in consequence
of this higher parentage and their habit through life of close association
with the nerve cells, they should be ranked above the simple glands.
If this be true, the chromaffine cell must be directly innervated by
"preganglionic" primary nerve fibres from the spinal cord and there
should be no intercalated ganglion cell relay. The adrenal medulla,
despite its glandular functions, would not belong to the peripheral gland
group but would lie on a level nearer to the central nervous system,

and be in reality a derivative of ganglion cells that had taken on
secreting functions.

The evidence that I wish to put forward on this point is not
conclusive, but it does suggest that ganglion cell relays are not present
on the glandular nerves.

It is a familiar observation that the intravenous injection of nicotine
into a cat completely abolishes all blood-pressure reaction to stimulation
of the splanchnics[1]. But nicotine does not hinder the response to
intravenous injection of adrenalin. Therefore nicotine must paralyse
the splanchnic nerves that should cause excretion of adrenalin.

It might be objected that the momentary stimulation caused by the
first injection of nicotine is so intense that it completely exhausts all
the available adrenalin, and leaves none to appear when the splanchnics
are subsequently faradised. That cannot be upheld. It is difficult to
exhaust the glands by nervous stimulation, and this certainly could not
be done by the transient stimulus of nicotine. As evidence on this
point may be quoted the following experiment. Both splanchnics were
cut within the thorax of a cat, from which the right superior cervical
ganglion had been removed three months previously. The peripheral end
of the left splanchnic was then stimulated; and the pupil dilated while
the ear vessels constricted in response to the adrenalin excreted. The
stimulation was repeated every five minutes, being on for three and off
for two minutes. After 80 minutes, that is with a total stimulation
of about 50 minutes, the left splanchnic could still cause some
adrenalin to be excreted and dilate the eye, though it was not so
effective as the resting right splanchnic. There was no ·difference
ultimately between the two glands in the depth of chromaffine stain.

The block caused by nicotine was proved by Langley to lie in the
ganglion cell relays. But that does not mean that the process of
necessity takes place in the ganglion cell as such, and that·the block
proves the presence of a ganglion cell. It may quite well be that the
stimulation and the paralysis by nicotine both occur in a part of the
innervated cell which has developed a peculiar biochemical sensitiveness
on account of the union with it of a preganglionic primary nerve from
the spinal cord[2], that is a receptive substance corresponding in its
features with the myoneural junction at the periphery. All the
primary synapses on the efferent paths outside the spinal cord show
this peculiar reaction to nicotine, and nicotine will consequently block

[1] Cf. details given by Langley. This *Journal*, xx. p. 223. 1896.
[2] Elliott. This *Journal*, xxxv. p. 437. 1907.

the splanchnic control of the adrenals whether the primary synapse be with a ganglion cell or directly with a chromaffine cell of the medulla.

The external nerves to the cat's adrenal are derived chiefly from the splanchnics, but also from small bundles which run directly to the gland from the lumbar sympathetic chain. Small and large masses of ganglion cells can always be found closely attached to the surface of the gland, especially at the hilum facing the semilunar ganglion, where the medulla often extrudes a sheet of chromaffine cells almost to the surface.

But the internal bundles of nerves, which run through the cortex and then break up into smaller leashes in the medulla, where they accompany the vessels and ultimately ramify among the nests of chromaffine cells, are chiefly myelinated. This can be easily recognised in frozen sections stained with haematoxylin and Scharlach, where the myelin sheath appears as a pink ring; and it is corroborated by the use of osmic acid. There is a rich supply of myelinated nerves, chiefly small and medium sized, to the medulla of the gland. Within the medulla ganglion cells are occasionally found, but in the cat they are very rare, and their number does not correspond with that which would be expected if the myelinated nerves were destined to unite with them.

The myelinated nerves might be postganglionic, for Langley has given several instances of the presence of a myelin sheath on postganglionic autonomic nerves. But this possibility was definitely excluded by the proof that the nerves degenerate into the very heart of the medulla after section of the splanchnic trunks.

By a lumbar incision the splanchnics were divided immediately below the diaphragm, that is at least a centimetre above the semilunar ganglion. The lateral nerves from the lumbar sympathetic chain were untouched. Nine to ten days later the cat was killed, and the gland, nerves, and ganglion stained with osmic acid.

Fragments of the nerves were first cut out and teased: in these extra-glandular nerves degeneration was found right up to the surface of the gland. There was, therefore, no cell relay in the semilunar ganglion. Next, an attempt was made to trace the degeneration within the gland itself. This presented difficulties, that were never quite removed. Osmic acid penetrates badly. It makes the tissue brittle, so that an entire section of the gland cannot be cut with such certainty as to give a series. Embedding in gelatine was found useless, because the process spoiled the sharpness of the osmic stain; and the same was the result with paraffin. The Marchi method also failed, insomuch as

the degenerated nerves could not be distinguished with certainty from the black stained granules of the cortical fat.

The clearest staining was that given by simple osmic acid, about 0·3 %, with or without preliminary fixation in formalin. Sections were cut with the Aschoff freezing microtome, the knife being wetted with water. The myelinated nerves are then seen in conspicuous black against the light brown background of the cortical cells. The bundles run right through the cortex, and break up in the medulla. Degeneration could be recognised with absolute certainty, where the bundles chanced to be cut parallel to their length. It extended into the medulla, and it affected all the nerve fibres of a bundle[1]. Some bundles escaped entirely, being presumably those of the lateral fibres from the lumbar sympathetic.

An attempt was made to ascertain whether any afferent fibres were present among the intra-glandular nerves, since it was possible that these might be the actual myelinated fibres in which degeneration was seen upon section of the splanchnics, whereas the efferent fibres might lose their myelin sheath below a supposed cell relay in the semilunar ganglion and so fail to be detected by the osmic stain. The latter possibility with regard to the efferent nerves could have been settled by cutting the anterior roots alone over several segments, and noting whether the degeneration extended into the gland as it does after section of the splanchnics. I preferred the direct method of tracing the afferent fibres themselves. This could not be done by Langley and Sherrington's method of cutting both posterior and anterior spinal roots and then counting the undegenerated fibres, because the total extent of the spinal root innervation of the adrenals was unknown. Instead of this, the posterior root ganglia themselves were excised without damage of the anterior roots. When the 5th, 6th, 7th and 8th thoracic ganglia were removed on one side, degeneration in the adrenal nerves did not result in two cats, although the splanchnics contained a very large number of degenerated fibres. These observations are too meagre to justify the total exclusion of afferent fibres. But they do serve to establish the important point that the intra-glandular myelinated nerves under discussion are not all afferent, and that therefore the argument from degenerative section of the splanchnics can be applied.

[1] Fusari, *Arch. Ital. de Biol.* XVI. p. 263. 1891, confirms the observations made by Bergmann (1839) and Gottschau (1883) that nerves may dive through the cortex of the gland, and emerging pass on to the semilunar ganglion. The degenerated bundles were not of this type.

CONCLUSION.

Section of the splanchnic nerves causes the myelinated nerves of the adrenal gland to degenerate up to their endings in the medulla. Since few, if any, of these glandular nerves are afferent, it is clear that the primary synapse of the efferent fibres must lie in the medulla. Here ganglion cells are rarely found[1], and the myelinated fibres seem to branch and run directly to the nests of chromaffine cells. So it appears probable that the latter are directly innervated from the primary " preganglionic " nerves without the intervention of a ganglion cell. Clear proof of this probability requires more detailed histological study than I have been able to make. It is necessary that special stains should be used to trace the degenerated nerves up to their terminal ramifications.

In the descriptions that have been given by pure histologists of the innervation of these glands, attention has not, so far as I am aware, been definitely paid to the question of how the ganglion cells are related to the entering nerves. Fusari and Dogiel[2] found that ganglion cells are rare in the medulla of the mouse and rat respectively, and Dogiel observed that they are rarer in the cat than in the rabbit. Giacomini[3], using the rapid Golgi method, described in birds a rich nervous supply to the medullary cells, while the cortical cells were almost naked of such. Numerous sympathetic cells were seen on the outside of the gland, but few within. The question of the ganglion cell relay was not clearly considered, but Giacomini decided against Kohn's view because the nerve terminations about the chromaffine cells resembled those found in ordinary gland cells rather than those in ganglion cell synapses.

[1] By a complete series of paraffin sections I examined the entire adrenal gland of a cat, but I failed to discover any true nerve ganglion cells within the medulla. Prejudice and the tediousness of the microscopic search make it possible that some ganglion cells were overlooked, but they must have been few; whereas the entering nerves are many. It appears, then, that in the cat a clearer separation of the chromaffine from the ganglion cells has taken place than in other animals, and consequently it becomes possible to trace the degenerated fibres to one or other type of cell. What might be regarded as a more primitive type is occasionally seen in accessory adrenals attached to one of the cat's splanchnic ganglia, where chromaffine cells and nerve cells are intermingled, but at the edge of the ganglion an offshoot of chromaffine tissue is capped by a mass of cortical cells, just as in the Monotremata. This *Journal*, XXXIV. p. 358. 1906.

[2] *Arch. f. Anat. u. Physiol.* Anat. Abtheil. p. 90. 1894.

[3] *Accad. dei Fisiocritici di Siena* Nov. 24. 1897.

With this reservation that the final microscopic proof is still needed, one would then place the medullary chromaffine cell on the same level as the sympathetic ganglion cell. Ganglion cell and "paraganglion" cell have a similar embryological derivation : they have a like innervation : and they have the same action on the peripheral tissue, which the one affects directly by the nervous impulse and the other by adrenalin excreted into the blood stream. Their present anatomical separation may be the index of a differentiation of functions which were once held by the two in common, when the adrenalin liberation was a part of the nervous impulse[1] and the "paraganglion" cell was a part of the ganglion cell.

[1] Elliott. This *Journal*, xxxi. *Proc. Physiol. Soc.* p. xx. 1904.

Pach 17-   A

The " P.-R." interval in human electrocardiograms and its relation to exercise[1]. By THOMAS LEWIS and THOMAS F. COTTON.

(From the Cardiographic Department, University College Hospital.)

Simple acceleration of the auricular rate, as induced by stimulation of the auricle with rhythmic induction shocks, usually has little effect upon the P.-R. interval (Lewis and Oppenheimer for the cat's heart; *Quart. Journ. of Med.* IV. 147. 1910–11). A trifling reduction of the P.-R. interval may be noticed in such experiments.

	Period of acceleration		Natural heart beat	
	P.-R.	Rate of heart	P.-R.	Rate of heart
1st experiment	·098*	184	·107	116
2nd experiment	·109	180	·121	110
	·110	168	·120	109

* Each figure in the tables is an average of three measurements; greatest error not greater than ·003 second. Measured with the Lucas microscopic comparator.

On the other hand, the effects of a similar auricular acceleration upon the interval, when conduction is already damaged, is very considerable; it leads immediately to a greatly enhanced degree of heart-block, as Lewis and Oppenheimer have shown.

Upon these and similar observations[2] the view was based that normally the special conducting tissues have a considerable reserve.

The immediate effects of brief and strenuous exercise, sufficient to produce laboured inspiration and considerable acceleration of the heart's action, is an almost constant reduction of the P.-R. interval. The reduction usually amounts to ·01–·03 secs. It may be due in part directly to acceleration: more probably it is the outcome of a sympathetic nerve effect upon the conducting tissues. The electro-cardiogram (lead II) is changed in form immediately after exercise; P and T are notably and almost constantly increased in amplitude, R is almost always decreased in amplitude, Q and S are less conspicuously increased. The conspicuous changes are precisely those which Rothberger and Winterberg (*Pflüger's Archiv*, CXXXV. 506. 1910) recorded in dogs upon stimulating the two stellate ganglia simultaneously.

As the rate after exercise falls to normal in the healthy subject, the length of the P.-R. interval quickly reverts to its original value (usually in three to five minutes). During the subsequent fall of heart rate normal values are maintained; it is the rule to find the original value maintained, but the intervals may decrease a little or increase a little.

[2] *Mechanism of the Heart Beat*, p. 234. London, 1911.

Such variations from the original have not exceeded 0·018 second in these observations.

In patients in whom there is a primary defect of conduction, the immediate effect of exercise is (Turnbull, *Heart*, II. 15. 1910; Lewis, *Heart*, II. 210. 1912) a decrease in the degree of the defect; this is, relatively, of considerable duration. When the rate falls after exercise, the impairment of conduction is most prominent and high grades of heart-block are often encountered (Turnbull and Mackenzie, *Heart*, II. 293, 353. 1911).

Name	Age	Before exercise		0—½ min. after exercise		½—1 min. after exercise		Form of exercise
		P.-R.	Rate	P.-R.	Rate	P.-R.	Rate	
E. P. C.	43	·20*	83	·18	136	·18	115	5 mins. with weights†.
C. L.	30	·14	103	·13	147	·13	137	5 mins. ball punching.
J. McI.	39	·136	92	·137	153	·140	144	5 mins. with weights.
M. Ka.	29	·148	81	·14	133	·149	120	5 mins. with weights.
M. Ki.	26	·166	68	·137	118	·158	89	5 mins. with weights·
S. G.	44	·190	69	·164	118	·168	109	3 minutes skipping.

Time in minutes	1. S. S. (aged 24)		2. C. (aged 25)		3. L. (aged 31)		4. A. J. W. (aged 29)		5. E. D. W. (aged 31)		6. A. C. S. C. (aged 26)	
	P.-R.	Rate	P.-R.	Rate	P.-R.	Rate	P.-R.	Rate	P.-R.	Rate	P.-R.	Rate
5 before	·146*	97	·160	86	·166	75	·144	75	·174	80	·153	55
0—½	·140	156	?·113	163	·150	147	·136	144	·177	142	·144	105
½—1	·148	150	·126	150	·154	135	·136	126	·179	138	·140	90
3	·146	126	·150	111	?·168	104	·144	105	·190	107	·145	83
5	·158	113	·157	107	·169	96	·141	100	·186	102	·151	78
7	·154	101	·160	107	·165	100	·137	103	·192	104	·150	76
9	·150	107	·154	103	·160	98	·140	94	·190	102	·155	77
11	·146	103	·154	100	·154	96	·144	94	·188	101	·150	77
13	·152	107	·156	97	·156	95	·141	92	·183	105	·149	71
15	·152	102	·160	92	·166	93	·142	85	·183	91	·152	74
17	·142 (interruption)	130	·152	94	·163	94	·139	96	·183	95	·146	71
19	·150	113	·156	96	·158	92	·142	86	·182	93	·150	70
21	—	—	—	—	·136	90	·145	92	·183	87	·151	73
23	—	—	—	—	·140	88	·144	90	·183	82	·152	74
25	—	—	—	—	·153	88	·142	86	—	—	·153	72
90	—	—	·168	76	·166	76	·143	83	—	—	—	—
	5 mins.† weight lifting.		5 mins. horizontal bars.		3 mins. horizontal and parallel bars.		Running upstairs (approx. 1500 KgM in 30 secs.).		5 mins. punching the ball.		5 mins. punching the ball.	

* The greatest error is less than ·01 second.

† The subject was thoroughly blown in each instance.

When the heart slows after exercise, inhibitory tone is probably increased, and while in the normal subject this is insufficient to retard conduction to an abnormal extent, on account of the functional reserve in the tissues concerned; yet, where conduction is primarily impaired, it is sufficient to produce very apparent disturbances in the form of heart-block.

A CONSIDERATION OF THE INFLUENCE OF THE FIRST COSTAL CARTILAGE ON APICAL TUBERCULOSIS, BASED ON A STUDY OF 402 SPECIMENS.*

By H. MORRISTON DAVIES, London.

THE invention of a new method of attack upon a problem which has resisted many generations of investigators is always a particularly interesting and valuable contribution to science. Even if the direct success of the new method is but meagre, the indirect value it has in stimulating research upon fresh lines may be very great. Unfortunately, however, the freshness of an original idea does not necessarily render it acceptable, but may lead to its being crushed by authoritative opinion as unworthy of consideration, or left to a localized group of supporters whose very enthusiasm is regarded by general opinion as being a further argument against the validity of the conception.

The suggestion originally propounded by Freund, of the close relationship and interdependence of abnormal changes in the first costal cartilage with apical pulmonary tuberculosis, has received both these methods of treatment. In 1858 and 1859, when Freund first enunciated his view, outside a small circle, practically no serious notice was taken of it, and during the next forty years very few contributions appeared upon the subject.

FIG. 1.—Male, aged 17. First costal cartilages normal. Movements at sternal angle 0°. Old and recent tuberculous lesions at the apices of both lungs.

The suggestion of the relationship of abnormal changes in the first rib cartilage and apical tubercle was then revived, and contributions ranging from short papers to lengthy monographs—mostly in German—began to appear, all affirming with almost equal enthusiasm the soundness of the hypothesis.
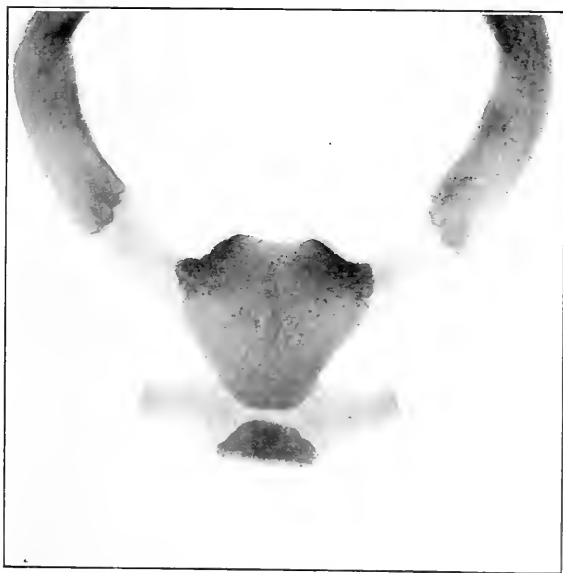
In 1858 and 1859, attention was first drawn by Freund to two types of abnormality in the chest wall, both of them affecting the costal cartilages of the ribs, and both directly predisposing to the development of secondary pulmonary lesions.

Both types produce their effects by causing fixation of the affected part of the thorax. In the one, ossification attacks the second, third, fourth, and fifth rib cartilages, and produces a fixation of the chest in the expanded position, with separation of the ribs, forward displacement of the sternum, and increase in the costal angle ; this is the condition known as rigid dilated thorax (starr dilatierte Thorax), with which bronchitis and emphysema are invariably associated as a secondary phenomenon. In the second type of abnormality the first costal cartilage alone is affected, being either ossified or abnormally short, and the fixation of the upper part of the chest which results is regarded as very strongly predisposing to apical tuberculosis. It has been shown that the ossified cartilage may fracture and a false joint develop between the fractured surfaces, and Freund has further elaborated his hypothesis to include the view that the restoration of movement to the upper thoracic opening by the false joint leads to the healing of the tubercle in the apex of the lung.
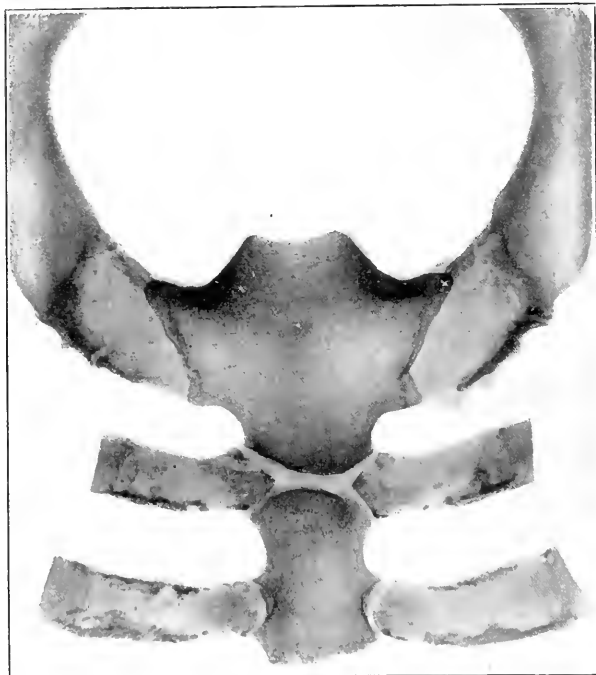

FIG. 2.—Male, aged 50. First costal cartilages show slight ossification. Note changes in second and third cartilages. Movement at sternal angle 7°. Lungs, right apex normal ; left shows healed apical tuberculous lesions.

Rigid Dilated Thorax.—The co-existence of the characteristic picture of the rigid dilated thorax with the pulmonary lesion of bronchitis and emphysema was easily determined, while the results of the operation of removing the affected cartilages, as seen in the cases shown at the Congress of the *Deutsche Gesellschaft für Chirurgie*, in Berlin, in 1910, were sufficiently encouraging to satisfy me that the operation was not only theoretically sound, but also practically efficient in greatly alleviating the distress of people suffering from this disease. The results which I have obtained from operating on patients so afflicted have served to strengthen this view. The further consideration of this group of cases is not within the scope of this paper.

The First Rib Cartilage.—Freund, holding the view that when tubercle had attacked the apex of the lung as a result of abnormal rigidity of the first rib cartilage, the tuberculous foci often healed if fracture of the cartilage occurred spontaneously, suggested that division of the affected cartilage should be undertaken for cases of active apical tuberculosis.

This operation seemed to me to be a rational procedure provided the premises were correct; but the evidence in support of these premises did not appear to me to be unexceptionable, and to satisfy myself, therefore, I undertook the investigation of the relationship of apical tuberculosis and abnormalities of the first costal cartilages.

This paper is not intended to be a critical review of the work of Freund, Hart and Harras, Rothschild, and others, who have studied the alterations in size, shape, and character of the ribs, cartilages, manubrium, and manubriosternal joint which contribute to the movement and form of the upper thoracic opening, but rather to give the results of my own observations.

The material on which my investigations were made consisted of :—

1. *Specimens from 201 autopsies.*

2. *One hundred radiograms.*

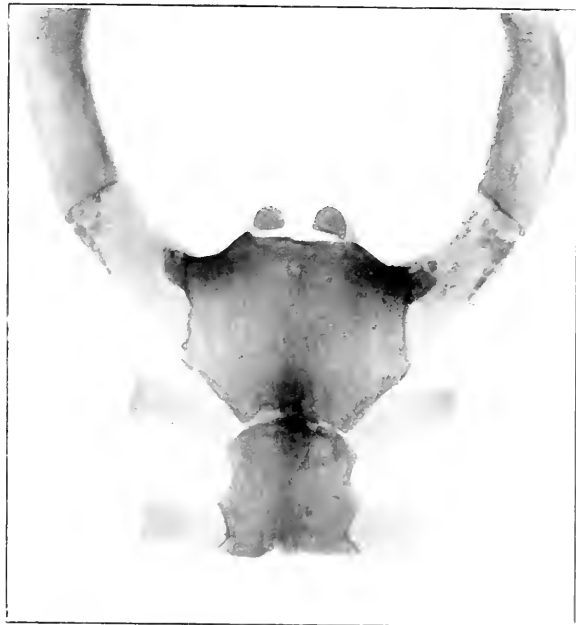3. *The thoracic skeleton and contents from seventeen monkeys.*

FIG. 3.—Male, aged 32. First costal cartilages show slight ossification. Movement at sternal angle 1. Large tuberculous cavities at the apices of both lungs.

1. **Specimens from 201 Autopsies.**—These consisted in the majority of cases of the manubrium sterni and upper part of the gladiolus, the first rib and costal cartilage, and the cartilages and adjacent parts of the second and third ribs, removed in one piece; in a certain number of the cases the gladiolus and first ribs and cartilages only were obtained. In every case the lungs were also reserved for examination. The skeletal portions were dissected clean of all soft parts, measurements were taken of the maximum breadth of the upper thoracic opening, as determined by the greatest width between the inner (and upper) borders of the first ribs, while the proportionate width of either side was obtained by laying the specimen so that the centre of the gladiolus and the centre of the suprasternal notch both rested on a straight line which was continued beyond them; measurements were then taken from this mesial line to the inner border of the first ribs at their maximum breadths. The sternal angle and the degree

of movement in it were noted. In some cases a radiogram was taken of the specimen. The whole specimen was next divided with a fret saw into an anterior and posterior segment. The cut surfaces allowed of accurate observation and measurement of the cartilages. The length of each cartilage was obtained by measuring from the mid-point (between the upper and lower borders) of the costo-chondral junction to the mid-point of the chondro-sternal junction. To study more fully the degree of ossification and the state of joint formation or fracture, antero-posterior vertical and horizontal sections were made through the cartilages. To record the degree of ossification of the cartilages, the terms "normal," "slight ossification," and "marked ossification," have been employed. The separation into the last two groups must necessarily be an artificial one, and based on one's individual standard. If ossification extended over both upper and lower borders and over the anterior surface (as in *Figs.* 4–6), the condition was called one of "marked ossification;" if, however, the ossification was in patches and limited (as in *Figs.* 2 and 3), the cartilages were described as showing "slight ossification." In a research such as this, when one recognizes that the separation of the description of the cartilages into groups labelled "slight" and "marked" ossification is to a certain extent an arbitrary one,

FIG. 4.—Male, aged 72. Marked ossification of both first costal cartilages. Right side, false joint at the costo-sternal juncture. Left side, false joint in middle of cartilage. No movement at sternal angle. The apices of both lungs normal.

and when one further realizes the insecurity of the decision whether an old healed scar at the apex of the lung is a tuberculous lesion or not, it is obvious that precautions must be taken to eliminate fallacy as far as possible from the judgment on each item of the material. For this reason the following routine in the examination of the specimens was adopted. The skeletal part was completely examined and recorded by me, while the condition of the lung, the presence or absence of old and healed or recent and active tubercle, was noted and recorded independently by Dr. Theile or Mr. Embleton, except in the case of the twenty-seven specimens from the City of London Hospital; this series was very kindly obtained for me by Dr. Gloyne, by whom the condition of the lung was recorded.

To Dr. Theile and Mr. Embleton, and to Dr. Gloyne, I tender my best thanks for the very great assistance they have been to me.

The range of movement at the angle of Ludovici was estimated by a goniometer. After the specimen had been divided into anterior and posterior portions, the condition of the union between manubrium and gladiolus and the presence or absence of a cavity in the fibro-cartilage, or of ossification, were noted.

The 201 specimens were obtained as follows :—

One hundred and twenty-seven were from autopsies at University College Hospital, on patients of ages ranging from twelve to eighty-two years. These were in no way selected.

Twenty-seven were from autopsies at the City of London Hospital for Diseases of the Chest, on patients from twelve to seventy-three years of age.

Twenty-two were from Infirmaries, and were selected cases inasmuch as they were consecutive cases of adults dead from pulmonary tuberculosis ; making a total of 176 specimens from males and females of over twelve years, and giving, therefore, for comparison and study, 352 first costal cartilages and a similar number of lungs.

The remaining twenty-five specimens were from a consecutive series of autopsies at University College Hospital, from children under twelve years of age.

2. **The Radiograms.** —In order to obtain further data on the relationship of

FIG. 5.—Female, aged 55. Marked ossification of both first costal cartilages. On either side false joint close to costo-chondral juncture. On right side healed fracture at costo-sternal juncture. No movement at the sternal angle. The apices of both lungs normal.

the ossification of the first costal cartilage to age and sex. 100 consecutive radiograms of the upper part of the chest (all of which had been taken for quite other purposes) were examined, the condition of the cartilages recorded, and the age and sex of the patient. The proportion of females in this series is smaller than I should wish, but in order to avoid selection the series was in no way altered.

3. **The Thorax and Contents of Seventeen Monkeys.**—I obtained from the Zoological Gardens the thorax of seventeen primates, of ages varying from about one to six years, in order to see whether ossification or alterations in length tended to predispose in these animals to apical pulmonary tuberculosis.

I should like to take this opportunity of thanking Dr. Chalmers Mitchell for the facilities he gave me for obtaining this series.

The views propounded by Freund are briefly as follows :—

The aeration and nutrition of the apices of the lungs are dependent on the movements of the upper part of the thorax (the upper thoracic opening), and the adequacy of these movements is to a great extent dependent on the length and elasticity of the first costal cartilages. During inspiration the raising of the sternum is associated with a torsion of these cartilages. The freedom of movement is necessarily, therefore, dependent on the capacity of these structures to undergo spiral rotation. Abnormal shortness or ossification in the costal cartilages must interfere with this capacity, and the aeration and nutrition of the
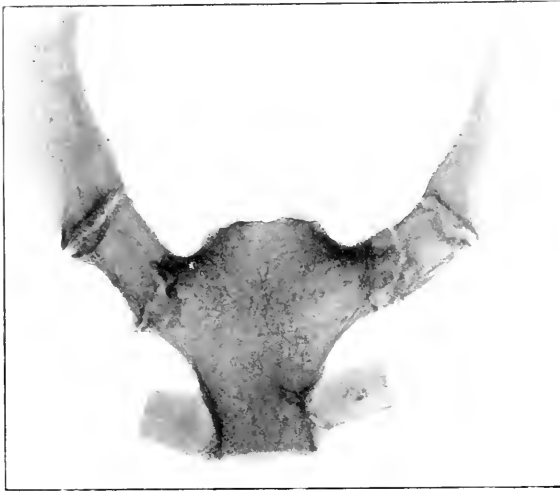

Fig. 6.—Male, aged 66. Marked ossification of both first costal cartilages. On the right side at the costo-chondral juncture there is a fracture that is practically healed. On the left side no fracture exists. (N.B.—The presence or absence of a false joint or fracture cannot be determined by radiographic examination alone.) The manubrium and sternum are directly continuous. Healed tuberculous lesions at the apices of both lungs.

lung is thereby interfered with and a predisposing factor for the development of tubercle established. Freund shows further, that the first rib and cartilage are intimately connected with the shoulder, clavicle, and scapula. If the cartilage does not develop fully, there is imperfect expansion of the upper part of the chest, and the condition known as "habitus phthisicus" occurs. As a result of the interference with the movements of the upper thoracic opening there is a compensatory hypertrophy of the scaleni, which in turn
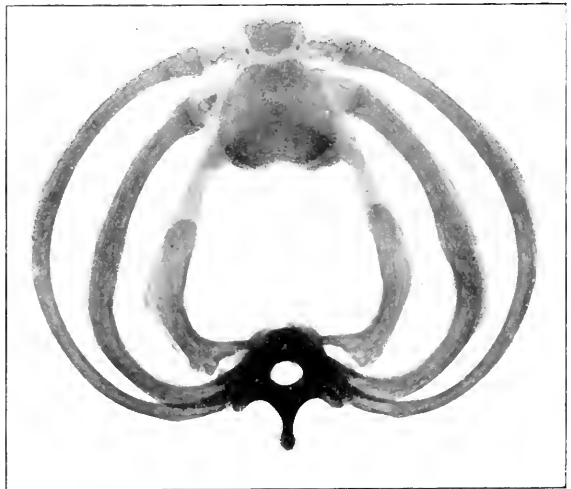

Fig. 7.—Chaema Baboon, aged about 4 years. No ossification in first costal cartilages. The apices of both lungs are normal.

leads to an inflammatory change in the perichondrium, and later, to ossification and complete rigidity of the first costal cartilage.

Freund not only maintains that the rigidity of the first rib cartilages is a strong predisposing factor to the development of apical tubercle, but further, that when fracture of the ossified cartilage occurs, with formation of a false joint, there is marked tendency for the apical tubercle to clear up.

Schmorl drew attention to the existence, in a certain proportion of cases, of a groove on the posterior and outer aspects of the apex of the lung caused by the pressure of the first rib, and showed that one of the three common places for apical tubercle to begin at, was in this groove. Freund regarded this as further evidence in support of his hypothesis.

The results of my investigations tend to show quite clearly that, whilst apical tuberculosis is found in people with abnormally short or ossified cartilages, this association is incidental only, and not one of cause and effect. Ossification found in the first costal cartilages is directly dependent on the age and sex of the subject.

The first difficulty that presented itself to me was the determination of what constitutes abnormal shortness in the first costal cartilage. Freund regards a length below 3 cm. as short for an adult male, and gives the average length as 3·8 cm. for a man, and 3·1 cm. for a woman. My figures work out at considerably less than this. In males an unossified first cartilage was found 44 times on the right side, average length 3·160 cm., and 44 times on the left, average length 3·294 cm. ; in females 50 times on the right side, average length 2·776 cm., and 51 times on the left, average length 2·885 cm. *Table I* on the following page gives the lengths of the normal and ossified cartilages (to the nearest decimal point) in the University College Hospital consecutive series of 125 cases. Three imperfectly developed cartilages are omitted.

This table shows the very striking fact that ossification is not only not more prone to develop in short cartilages, but that the ossified cartilages include the longest in the series. One cartilage is recorded of 0·75 cm. in length, and one of 1·25 cm. ; in both of these the extreme shortness is apparent only, and is due to the extensiveness of the ossification which has replaced the cartilage. In the tables given in this paper a short cartilage is arbitrarily taken to mean one below 2·5 cm. in length. Out of 247 specimens in *Table I*, twenty-eight cartilages were below this standard of length. Thus 11·3 per cent would come in the class "abnormally short."

In *Table II*, *p. 9*, is shown the relative frequency with which normal lung or healed or active apical pulmonary tuberculosis was found in association with the various types of changes in the first costal cartilages. The figures are obtained from the 125 consecutive cases from University College Hospital ; twenty-two cases from the Infirmaries ; twenty-seven cases from the City of London Hospital. The cases excluded from this list are the series of twenty-five children from University College Hospital and two cases in which there was marked abnormality in the development of the cartilage.

A careful study of this table will show that there is no decided association of any particular form of change as regards ossification or abnormality in length with either healed or active tuberculous lesions of the lung. It will be seen, indeed, that in the male group only 56·0 per cent of the cartilages found in association

with a normal apex showed no abnormality, while in the female series the proportion of normal cartilages in conjunction with normal lung or with active apical tuberculosis, is almost the same (74·6 and 75 per cent).

Table I.—Giving the Lengths of the Normal and Ossified Cartilages

Size in cms.	Sex	Normal Cartilages	Ossified Cartilages
4·25	M.	—	1
	F.		
4·0	M.	1	3
	F.	—	—
3·75	M.	7	7
	F.	—	
3·5	M.	21	17
	F.	6	4
3·25	M.	12	9
	F.	12	3
3·0	M.	9	13
	F.	19	7
2·75	M.	4	13
	F.	16	4
2.5	M.	5	3
	F.	14	9
2·25	M.	2	5
	F.	9	2
2·0	M.	—	1
	F.	5	—
1·75	M.	—	—
	F.	2	—
1·5	M.	—	—
	F.	—	—
1·25	M.	—	—
	F.	—	1
1·	M.	—	—
	F.	—	—
0·75	M.	—	—
	F.		1
	Total	145	102

If now one considers this same series of cases divided into three groups according to age (Table III)—Group 1, ages 10 to 30 ; Group 2, ages 31 to 50 ;

and Group 3, ages 51 to 82—it will be seen that with advancing years there is an increase in the number of cases showing healed and active tuberculous lesions at the apex, the percentage of these cases to the total number in each group being 45·3, 57·6, and 72·4 in groups 1, 2, and 3 respectively. This increase bears no comparison, however, with that shown by taking the percentage of abnormal cartilages found in conjunction with healed and active disease at the apex, in the three groups. The figures are 18 per cent in Group 1, 50 per cent in Group 2, and 85·5 per cent in Group 3.

Table II.—SHOWING THE RELATIONSHIP OF NORMAL LUNG, HEALED TUBERCLE, AND ACTIVE TUBERCLE IN THE APEX OF THE LUNG, TO THE CONDITION OF THE CARTILAGE IN 174 CASES.

SEX	TOTAL	CONDITION OF LUNG	CONDITION OF THE FIRST COSTAL CARTILAGE.										
			Normal	Short normal	Short normal with joint	Slight ossification	Short slight ossification	Slight ossification with joint	Marked ossification	Short marked ossification	Short marked ossification with joint	Marked ossification with joint	Percentage of normal to abnormal
M.	82	Normal	46	2	—	15	—	—	15	—		4	56·6
F.	71		53	7	1	5	1	2		—	1	1	74·6
M.	91	Healed tubercle	24	3		32	1	5	9	—	3	14	23·6
F.	56		31	6	—	4	—	5	1	1	—	6	55·3
M.	61	Active tubercle	22	1	—	16	-	3	11	1	—	7	36·0
F.	24		18	1	—	1	-	2	2	-		—	75·0

The total in this table exceeds the number of cases, as whenever both healed and active lesions were found, the condition of the cartilage is given under each heading.

*Table III*—THE SAME AS *Table II*, BUT THE CASES ARE DIVIDED INTO AGE GROUPS.

SEX	TOTAL	CONDITION OF LUNG	CONDITION OF FIRST COSTAL CARTILAGE									
			Normal	Short normal	Short normal with joint	Slight ossification	Short slight ossification	Slight ossification with joint	Marked ossification	Short marked ossification	Short marked ossification with joint	Marked ossification with joint
		Ages 10 to 30.										
M.	23	Normal	21	2	—	—						
F.	24		22	2	—							—
M.	9	Healed tubercle	6			3						
F.	6		5	1								
M.	18	Active tubercle	16			2						
F.	8		7	1								

Table III—continued.

Sex	Total	Condition of Lung	Normal	Short normal	Short normal with joint	Slight ossification	Short slight ossification	Slight ossification with joint	Marked ossification	Short marked ossification	Short marked ossification with joint	Marked ossification with joint
Ages 31 to 50.												
M.	37	Normal	18	—	--	11	--	—	8	—	—	—
F.	32	Normal	23	3	1	3	—	2	—	—	—	—
M.	28	Healed tubercle	9	3		12	--	2	1	--	--	1
F.	31	Healed tubercle	21	2	--	1	—	4	1	--		—
M.	22	Active tubercle	6	1	--	10		2	2	-	--	1
F.	13	Active tubercle	11	-			—		2	—		
Ages 51 to 82.												
M	22	Normal	7	--	—	4	--		7	--	—	4
F.	15	Normal	8	2	--	2	1	—	--		1	1
M.	54	Healed tubercle	9			17	1	3	8		3	13
F.	19	Healed tubercle	5	3		3	--	1	—	1		6
M	21	Active tubercle			--	4	—	1	9	1	--	6
F	3	Active tubercle				1	—	2	--			

Table IV —(UNIVERSITY COLLEGE HOSPITAL SERIES OF 125 CONSECUTIVE CASES) SHOWING THE INCREASE OF OSSIFICATION WITH INCREASE IN AGE.
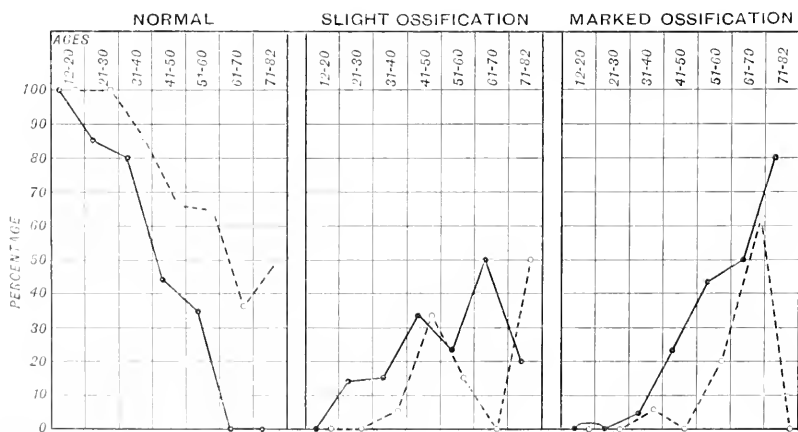
* The full line denotes the percentage in the male subjects, the dotted line the percentage in the female subjects.

It is this striking increase in the proportion of abnormal to normal cartilages with increase in age which offers a suggestion as to the cause of ossification in the cartilages.

A glance at *Table IV* must at once make it apparent that ossification of the first costal cartilage develops earlier and to a greater extent in men than women, and that increase in age is associated with an increase in ossification.

To test these results, 100 consecutive radiograms of the upper part of the chest, taken for quite other reasons, were examined, and the condition of the cartilage was noted; the age and sex of each of the patients were then looked up, and the records are shown in *Table V*.
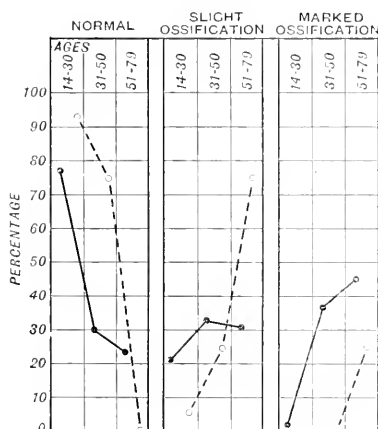
Table V.   *Table VI.*
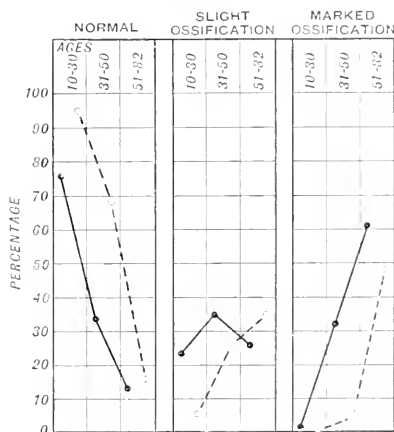
Lastly, *Table VI* shows this age, sex, and ossification relationship in 748 cases, composed of the 450 cartilages above recorded, together with the 98 cartilages from the City of London Hospital and Infirmary series, and 200 cartilages the details of which are given by Jungman (*Frankf. Zeitsch. f. Path.*, Bd. 3, s. 938).

Thus it will be seen that in both sexes, with increase in age there is a steady decrease in the number of normal first cartilages and a steady increase in the number showing marked ossification. In the male, the percentage of cartilages showing slight ossification increases up to middle life, and then decreases again, this latter change coinciding with the rise in the percentage of cartilages showing marked ossification. In the female, on the other hand, the percentage of cartilages with slight ossification increases steadily throughout life.

The Manubrio-sternal Joint.—Keith says that "the manubrio-sternal joint must be counted amongst the important respiratory joints." Absence of movement at this sternal articulation favours, in Rothschild's opinion, the development of apical tuberculosis, by limiting the movements of the upper thoracic opening. Freedom of movement undoubtedly facilitates expansion of the apex of the lung, but the absence of it does not appear to me to predispose to apical tuberculosis.

In 74 cases the range of movement obtained in the fresh specimen varied from 0° to 22°, the average being just over 4°.

In *Table VII* is shown the relative proportion of the various changes in the first costal cartilage to normal, healed, and active tuberculosis of the apex in the 74 cases in which the degree of movement of the sternal angle was noted. The table is divided into two parts : *Part A*, cases with movement at the sternal angle of 6° or more ; and *Part B*, cases with movement of 5° or less. The ages recorded are from 14 to 75.

Table VII.—Showing the Influence of Movement of the Sternal Angle.

Part A.—*Cases in which Sternal Angle shows movement of 6° or more.*

SEX	TOTAL	PERCENTAGE	CONDITION OF LUNG	Normal	Short normal	Short normal with joint	Slight ossification	Short slight ossification	Slight ossification with joint	Marked ossification	Short marked ossification	Short marked ossification with joint	Marked ossification with joint
M.	12	44·7	Normal	8	—	...	4	—	—	—	—	—	—
F.	9			6	—	—	3	—					
M.	13	47·5	Healed tubercle	7			5	1		—	—		—
F.	7			7									
M.	2	12·8	Active tubercle	—	—		2			—	—	—	—
F.	4			4									

Part B.—*Cases in which Sternal Angle shows movement of 5° or less.*

SEX	TOTAL	PERCENTAGE	CONDITION OF LUNG	Normal	Short normal	Short normal with joint	Slight ossification	Short slight ossification	Slight ossification with joint	Marked ossification	Short marked ossification	Short marked ossification with joint	Marked ossification with joint
M.	27	46·0	Normal	12	—	—	3	—	—	8	—	—	4
F.	24			18	3	—	1	—	—	—	—	1	1
M.	23	43·2	Healed tubercle	6	—	—	0	—	1	4	—	2	4
F.	25			14	2	—	2	—	5	1		—	2
M.	0	10·8	Active tubercle	2	—	—			—	2	—		2
F.	6			3	1		—	—	—	2	—	—	—

The first point to which attention must be directed in this table is the fact that the percentage of cases of normal lung and of healed and active apical lesions is practically the same in both series, i.e., in *Part A*, in which the movement at the sternal angle is above the average, and *Part B*, in which the movement is below the average, such difference as does exist being as a matter of fact in the direction of fewer cases of active tuberculosis in association with those cases where the range of movement of the sternal angle was 5° or less.

The most striking fact, however, is the total absence of marked ossification changes in the cartilages of those cases with a movement at the sternal angle of 6° or more, and the presence of these changes, in considerable number, in the

cases with a movement of 5° or less. But this phenomenon is explained in *Table VIII*, in which the cases are divided into age groups, and in which it will be seen that the great majority of patients with a movement at the sternal angle of less than 5° are elderly.

Table VIII.—PROPORTION OF CASES OUT OF 74 IN WHICH MOVEMENT AT STERNAL ANGLE IS 6° OR MORE, OR 5° OR LESS, ACCORDING TO AGE.

SEX	TOTAL	MOVEMENT 6° OR OVER	MOVEMENT 5° OR UNDER		AGES
M.	8	4	4	} 62·5%	14 to 30 years
F.	8	2	6		
M.	13	6	7	} 66 %	31 to 50 years
F.	19	6	13		
M.	20	3	17	} 88·4%	51 to 75 years
F.	6	0	6		

I have already shown that the extent of ossification of the first costal cartilage is directly dependent on the age and sex of the patient, and *Table VIII* shows that while 62·5 of the cases under 31 years have a range of movement in the sternal angle of less than 5°, and 66 per cent of the cases between the ages of 31 and 50, no less than 88·4 per cent of people over 50 years old show this limitation of movement in the sternal angle.

In 14 cases there was no movement at all obtainable in the sternal angle. One of these was a woman of 21, one was a woman aged 32, and the remaining twelve were over 50 years old. In the 28 lungs from these cases, active apical tuberculosis was found in 4, healed tuberculous lesions in 13, and the lung was normal in 11; this despite the fact that the associated first costal cartilages showed marked ossification in 14, slight ossification in 6, and no ossification in 8; and of these latter 1 was 2·5 cm., and another only 2·1 cm. long.

CAUSATION.—Freund has shown that the ossification involves mainly the anterior aspect and the upper and lower borders of the first costal cartilage, and considers the immediate cause of the process to be the constant pull of the scaleni muscles and the resultant irritation of the perichondrium. While disagreeing with Freund as to the reason for this constant straining action of the muscles, I think that it is quite probable that the ossification is due to a long-continued very slight irritating action, not only of the scaleni muscles, but also of the inter-costals of the first space and of the subclavius muscle and costo-coracoid liga-ment, both of which are inserted into the anterior aspect of the first cartilage. The evidence that the condition of ossification develops with increasing years and is more marked in the male than in the female, indicates that the primary cause is probably directly connected with occupation, and is not dependent on such a factor as length, which should exercise equal influence in the two sexes.

The "Schmorl" Groove.—Schmorl called attention to the occasional presence of a groove on the posterior and outer aspect of the lung at the level

of the first rib, and Freund considers that this groove is caused by the pressure of the rib as a result of the diminution of the size of the upper opening of the thorax from abnormal shortening of the costal cartilage.

Certain criticisms at once present themselves. The hypothesis seems to suggest that the size of the lung is predetermined, and that had the first costal cartilage been of average length, the lung would have fitted comfortably into the upper opening ; but that during development, the first cartilage had not attained its correct length, and the lung is constricted therefore by the rib. Such a method, however, does not accord with the general principles of development ; but rather an apparent constriction of the lung at the upper opening and an " overflow " above and below the first rib, is what would be expected if the lung were to increase in size after development had ceased, as in emphysema. *Table IX*, which records the presence or absence of a groove on the surface of the lung and the size of the cartilages in 119 specimens, does not in any way support Freund's hypothesis.

Table IX.— SHOWING THE PRESENCE OR ABSENCE OF A GROOVE ON THE LUNG AND THE SIZE OF THE CARTILAGES.

SEX	CARTILAGES SIZE	Lungs		SEX	CARTILAGES SIZE	Lungs	
		GROOVED	NOT GROOVED			GROOVED	NOT GROOVED
M.	2·5 cm. and over	32	37	M.	3 cm. and over	27	27
F.		17	22	F.		12	11
	Total	49	59		Total	39	38
M.	Under 2·5 cm.	1	3	M.	Under 3 cm.	7	14
F.		5	2	F.		10	11
	Total	6	5		Total	17	25

In the specimens from children ranging in age from eleven days to ten years, the average length of the first costal cartilage was 2·07 cm. in the right, and 2·12 cm. on the left side. The shortest was in a male three weeks old, the length of the right cartilage being 1 cm., and of the left 1·25 cm. Active tubercle was found at the right apex of a girl one year old with a cartilage 2 cm. long, and healed tubercle was found at the left apex of a boy aged eight, and at the right apex of a girl aged ten years. In both cases the corresponding cartilage was above the average length.

No evidence of any ossification was found in the cartilages of the seventeen primates examined, although both first costal cartilages of a female white-cheeked mangaby, aged about six years, showed central calcification.

SUMMARY.

1. Neither abnormal shortness nor ossification in the first costal cartilage predisposes to apical pulmonary tuberculosis.

2. Abnormal shortness of the first costal cartilage does not encourage ossification in that cartilage.

3. Ossification in the first costal cartilages is dependent on age and sex, and probably occupation.

4. With increasing age, there is increasing limitation of movement of the sternal angle.

5. Limitation of movement of the sternal angle does not predispose to apical pulmonary tuberculosis.

6. The presence of a groove in the posterior external aspect of the lung below the apex (Schmorl) is not the result of abnormal shortness of the costal cartilage, but probably of emphysema.

7. The formation of a false joint in the rigid cartilage does not tend to lead to the cure of apical tuberculosis : and therefore

8. The balance of evidence is against the probability of the operation for division of the first costal cartilage in cases of apical tuberculosis producing any material improvement.

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